# Genetic Architecture of Brain and Heart

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https://www.med.unc.edu/big-s2

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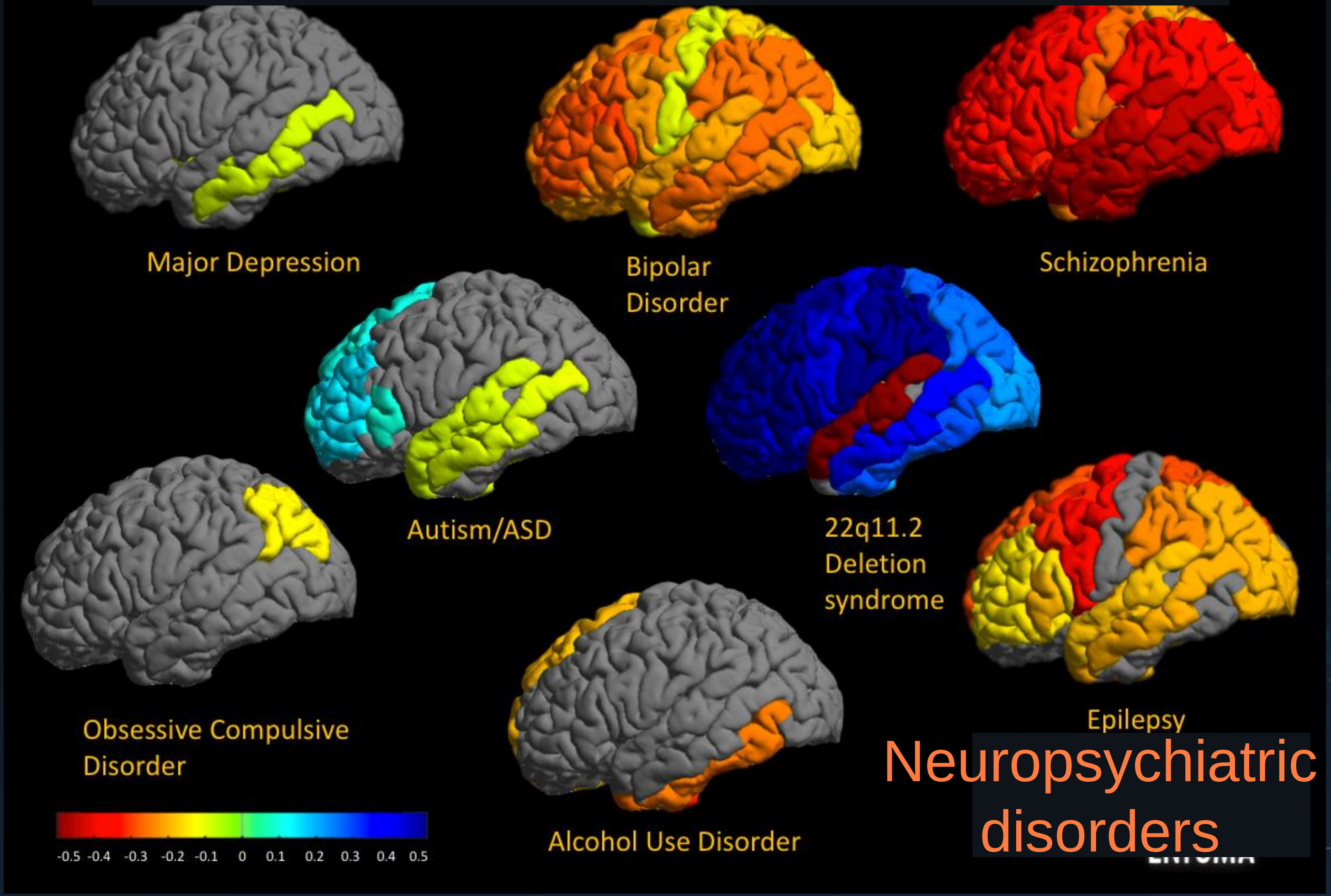
# Part I

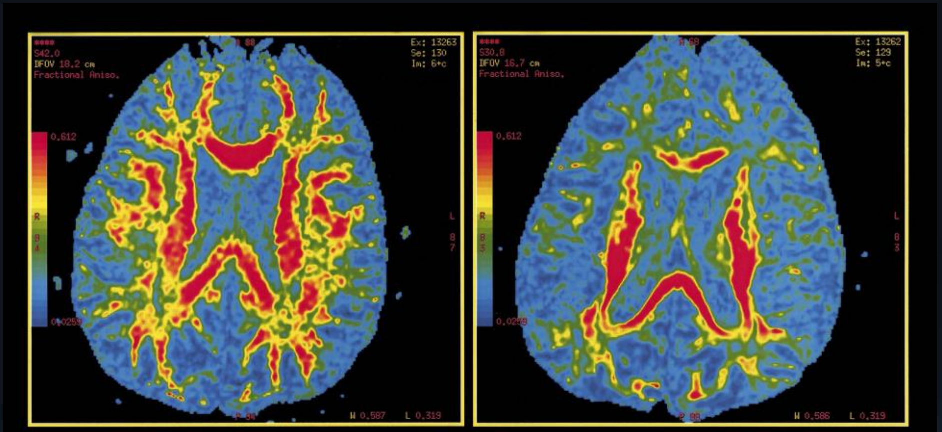
## Genetic Architecture of the Brain

# Brain Imaging for Brain Disorders

Capture the brain structure and function changes associated with major brain-related disorders and normal development

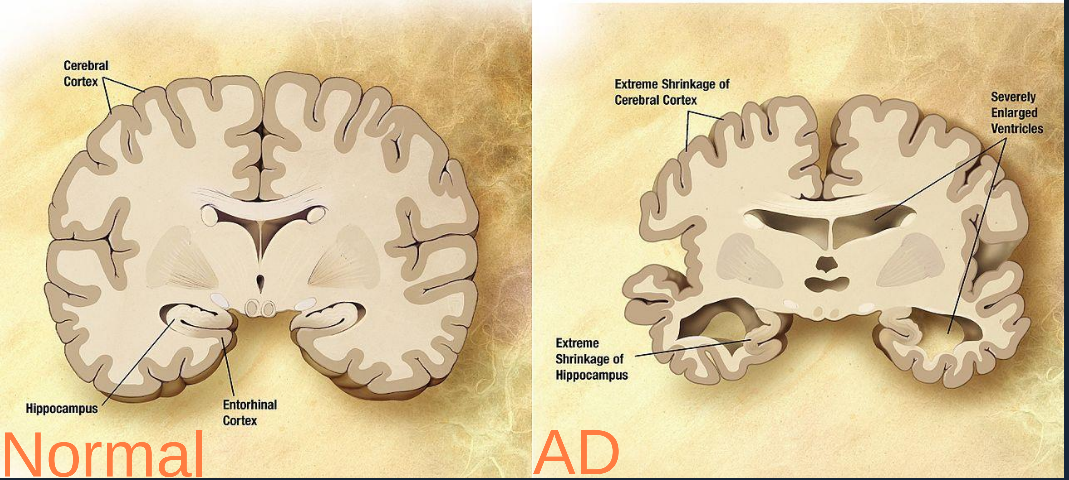



Neuropsychiatric disorders



Normal AD

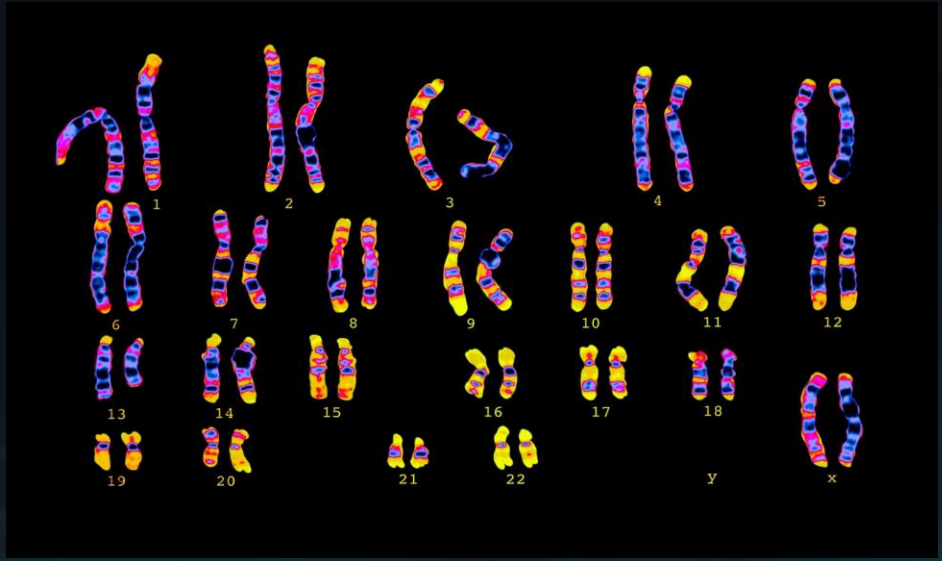
Alzheimer’s disease (AD) is associated with brain shrinkage

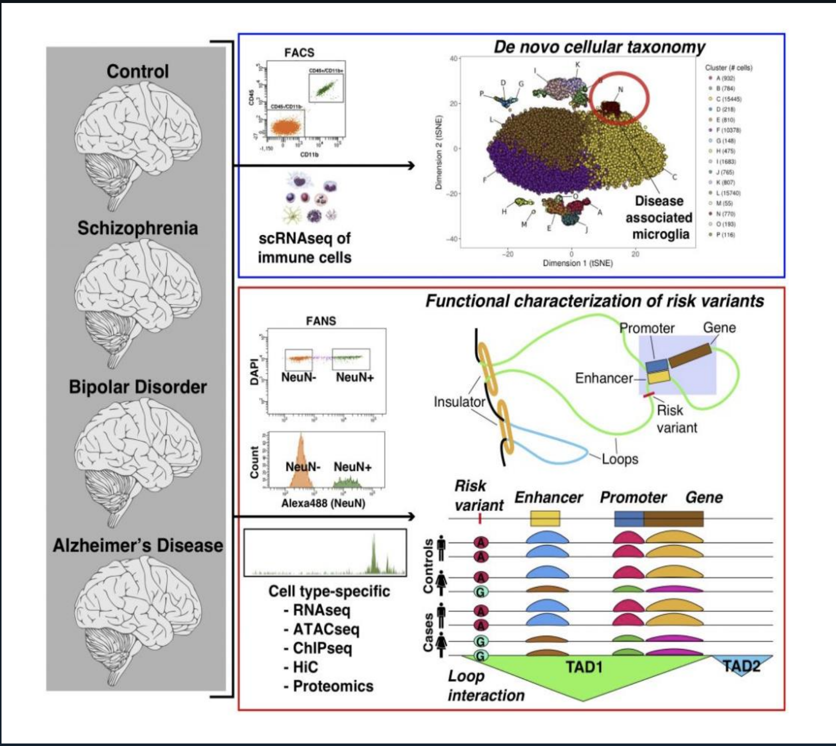


# Genetics of Brain Disorders

## Most major brain disorders (like AD) are **heritable complex traits/diseases**

Together 50%-70% of AD risk
75%-90% of ADHD risk
60%-85% of Schizophrenia risk
~80% of Autism Spectrum Disorder (ASD) risk




## Complex traits/diseases (many genes, environmental factors, complex functional mechanism)

Genetic signals are non-spare and weak:
Need large sample size to detect weak signals


Many genes contribute to the risk of AD
(polygenic genetic architecture)
(small but nonzero contribution)

# “Big Data” Imaging Cohorts

“Big data” Brain imaging datasets become available in recent few years

Systematically collect publicly available individual-level data for **> 120k** individuals

Build the largest database in this field

**Aging Brain**

**Brain Development**

BCP *(Age [0,5])*

PING *(Age [3,21])*

**ABCD *(n ~ 10k, Age [9,11])***

PNC *(Age [14,29])*

HCP *(Age [22,35])*

**UK Biobank *(n ~ 100k [Ongoing], Age [40,69]))***

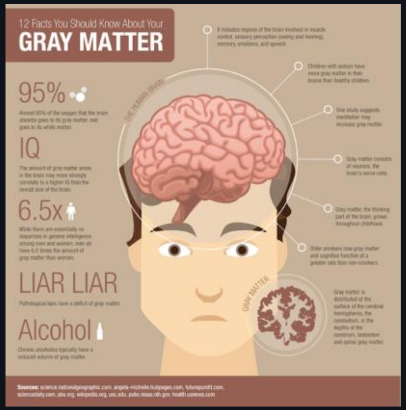
RADC *(Age > 65)*

ADNI *(Age [55,92])*

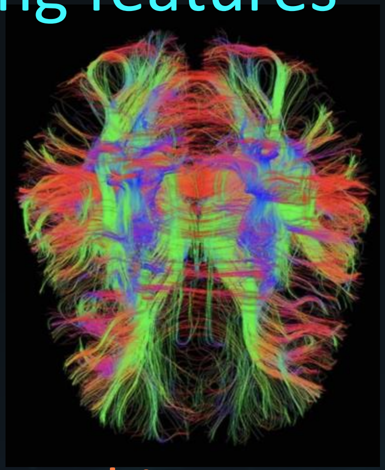
IMAGEN *(Age [14,22])*

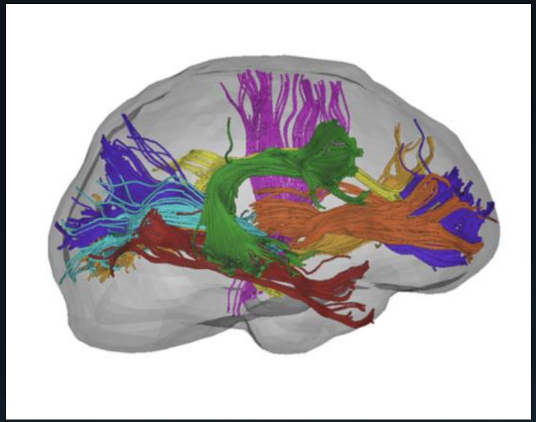
# Brain Imaging Modality Examples

## Harmonize tools/pipelines to consistently generate the full spectrum of neuroimaging features

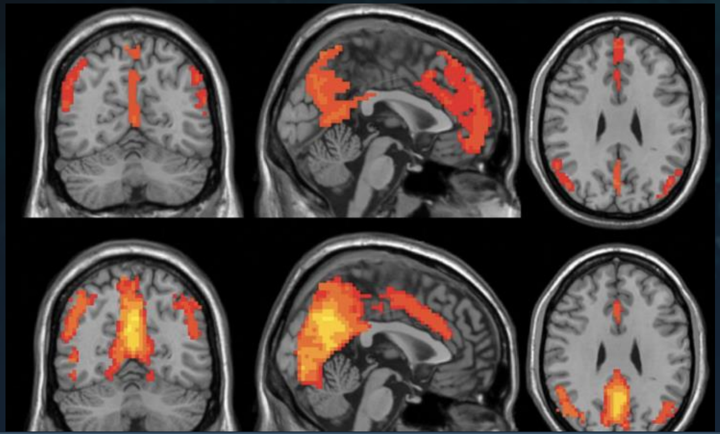



Cortical and subcortical structures





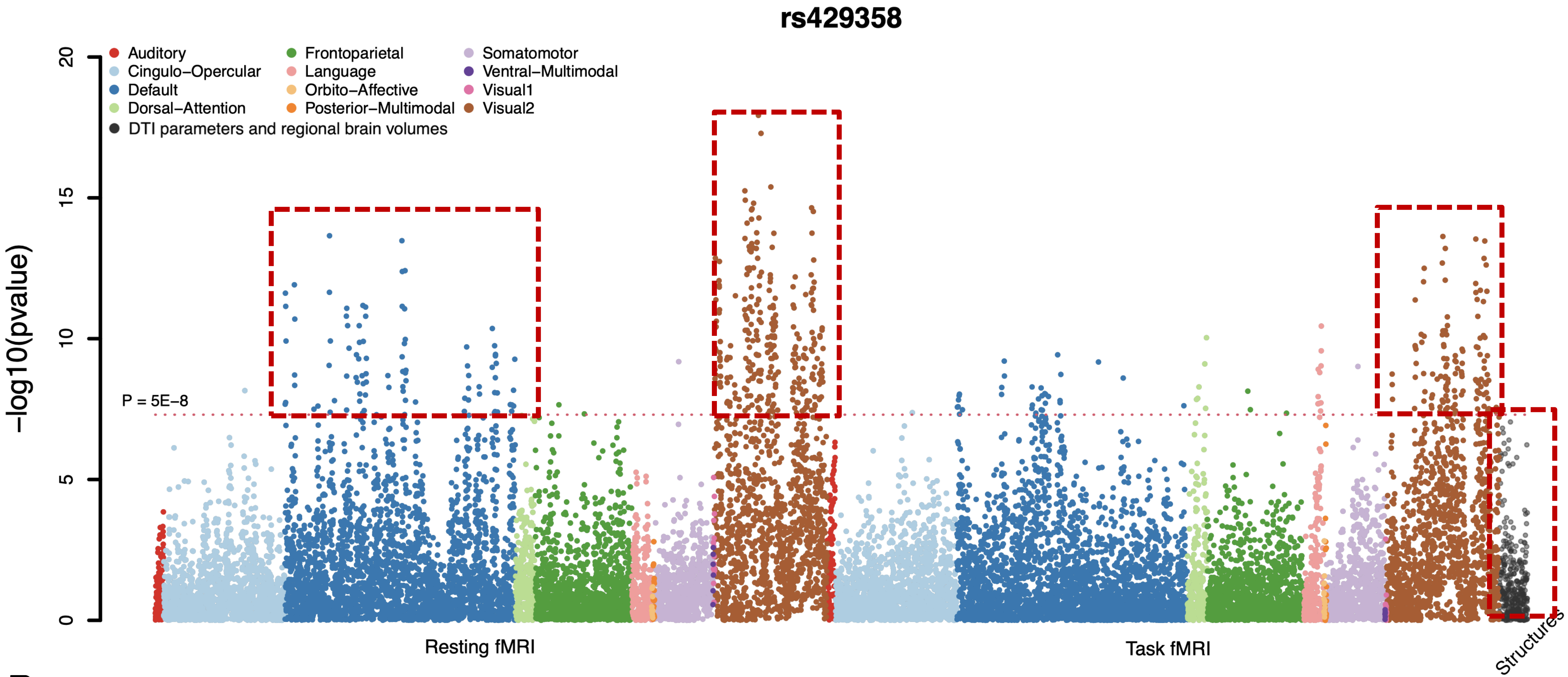
White matter microstructure
(Structural connectivity, diffusion MRI)



Functional networks
(Functional connectivity, functional MRI)

# APOE-associations across functional networks

observations: 1) Enriched in the secondary visual and default mode networks;
2) Stronger connections in fMRI than in structural MRI.



# It's just a beginning

**Publications (2018+)**

Heart–brain connections: Phenotypic and genetic insights from magnetic resonance images. *Science* 380, abn6598 (2023). LINK.

Genetic influences on the shape of brain ventricular and subcortical structures (2022). **medRxiv**,

Common variants contribute to intrinsic human brain function networks (2022). *Nature Genetics*.

Genetic influences on the intrinsic and extrinsic functional organizations of the cerebral cortex (2021). **medRxiv**, 21261187. LINK

Common genetic variation influencing human white matter microstructure (2021). *Science*, 372–6548. LINK

Transcriptome–wide association analysis of brain structures yields insights into pleiotropy with complex neuropsychiatric traits (2021). *Nature Communications*, 842872. LINK

Genome–wide association analysis of 19,629 individuals identifies variants influencing regional brain v[illegible] –architecture with cognitive and mental health traits (2019). *Nature Genetics*, 51(11), 1637–1644. LINK

Large–scale GWAS reveals genetic architecture of brain white matter microstructure and genetic overlap [illegible] traits (n= 17,706) (2019). *Molecular Psychiatry*, in press. LINK

Heritability of regional brain volumes in large–scale neuroimaging and genetic studies (2018). *Cerebral Cortex*, 29(7), 2904–2914. LINK

Hundreds of associated genetic variants for 2100+ neuroimaging traits across six modalities: (grey matter volume, white matter microstructure, resting-state functional connectivity+fMRI, task fMRI, shape, heart )

**We make our research results publicly available by building the following resources.**

**If you are interested in other summary–level data from our analyses or have any questions or comments, feel free to contact Bingxin Zhao (bingxin@purdue.edu) or Hongtu Zhu (htzhu@email.unc.edu).**

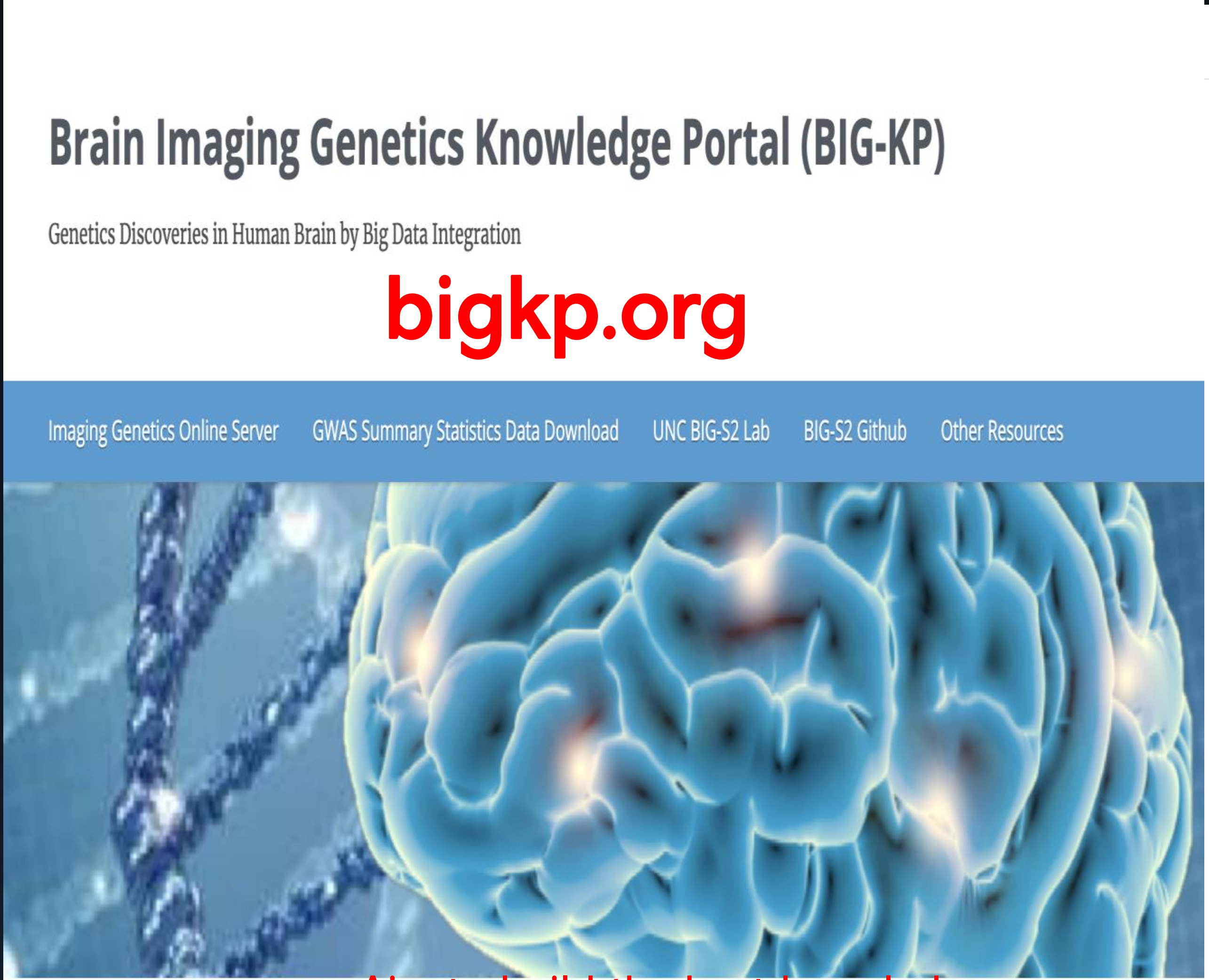
## 1. Imaging Genetics Online Server

We build a GWAS browser using the PheWeb tool to explore GWAS results for massive functional, structural, and diffusion neuroimaging traits. Currently, we support GWAS results of 2104 traits trained in the UKB British cohort (n~34,000), including

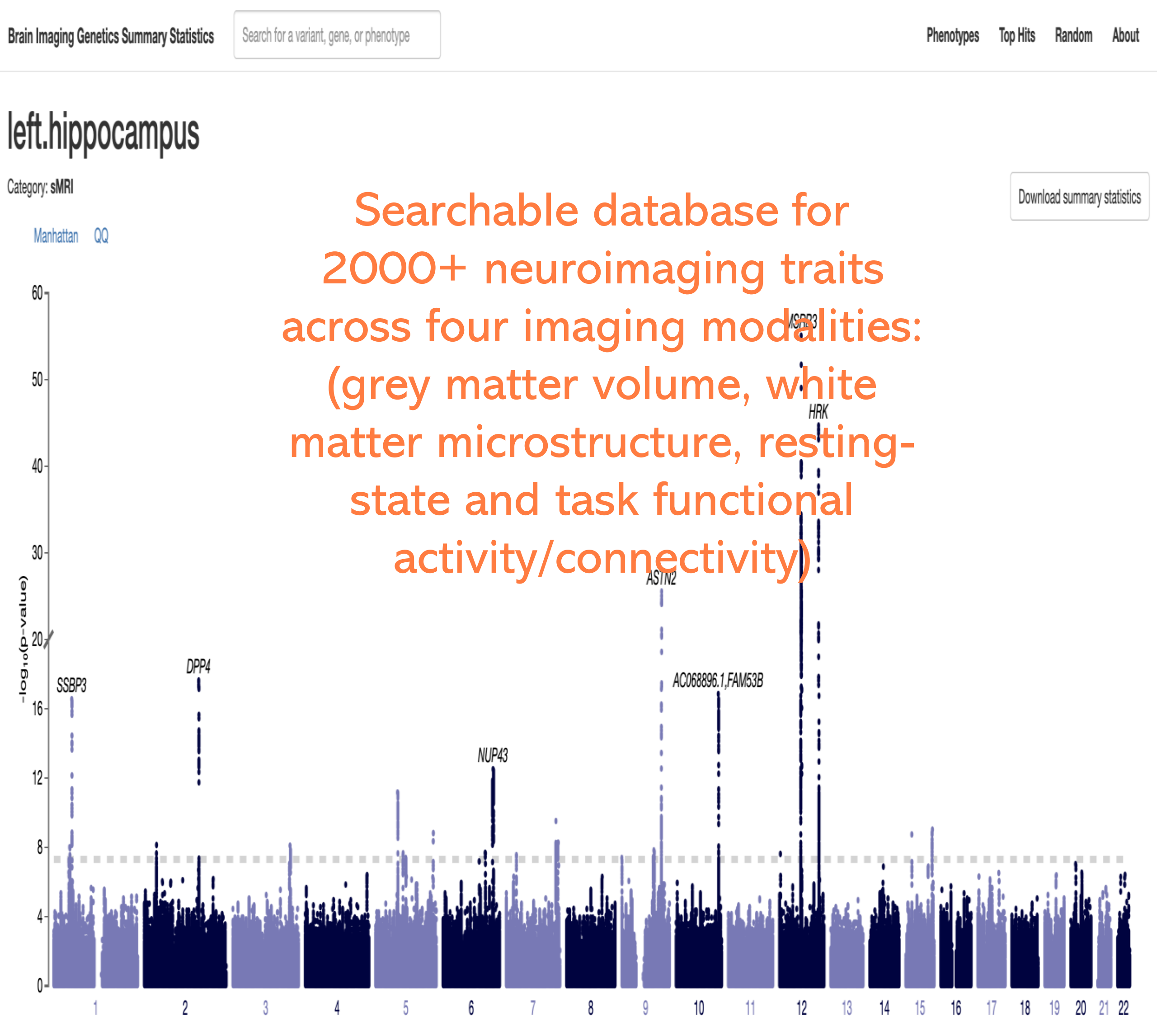
1. 635 ENIGMA–DTI parameters of brain white matter **(diffusion MRI)**
2. 376 ANTS regional brain volumes **(structural MRI)**
3. 191 ICA–based functional MRI traits (rs–fMRI(ICA))
4. 309 parcellation–based functional MRI (task/rs–fMRI(Glasser360))

**Genetics discovery in human brain by big data integration**

# Brain Imaging Genetics Knowledge Portal




Aim to build the best knowledge database of neuroimaging genetics

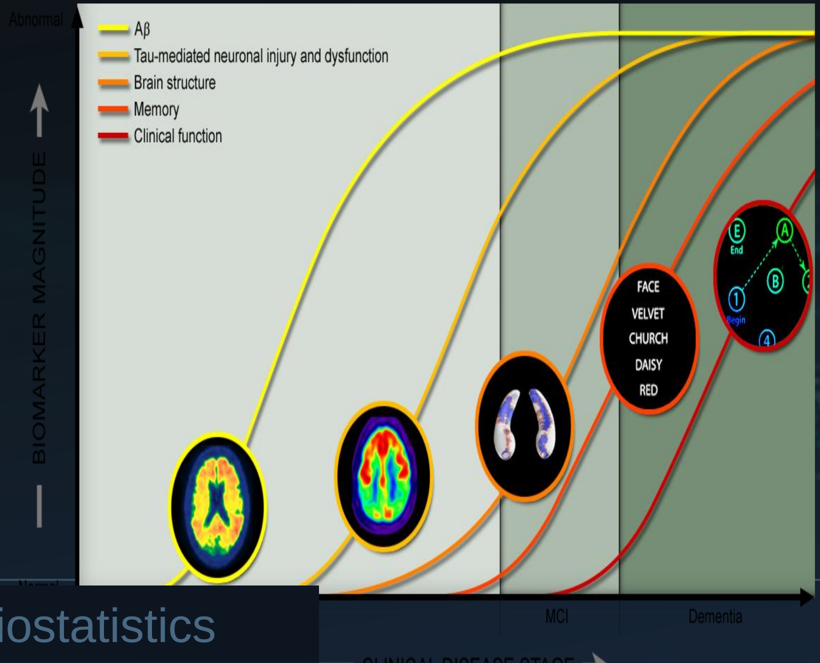


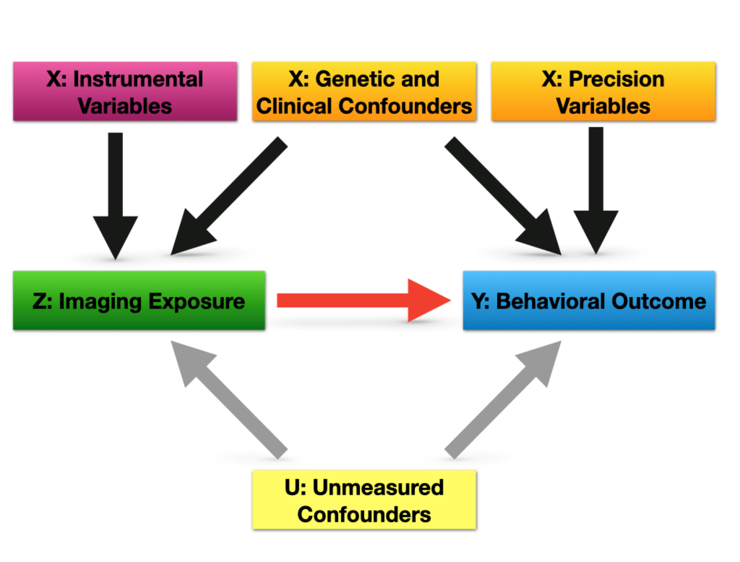

Searchable database for 2000+ neuroimaging traits across four imaging modalities: (grey matter volume, white matter microstructure, resting-state and task functional activity/connectivity)

# Why Imaging Traits?

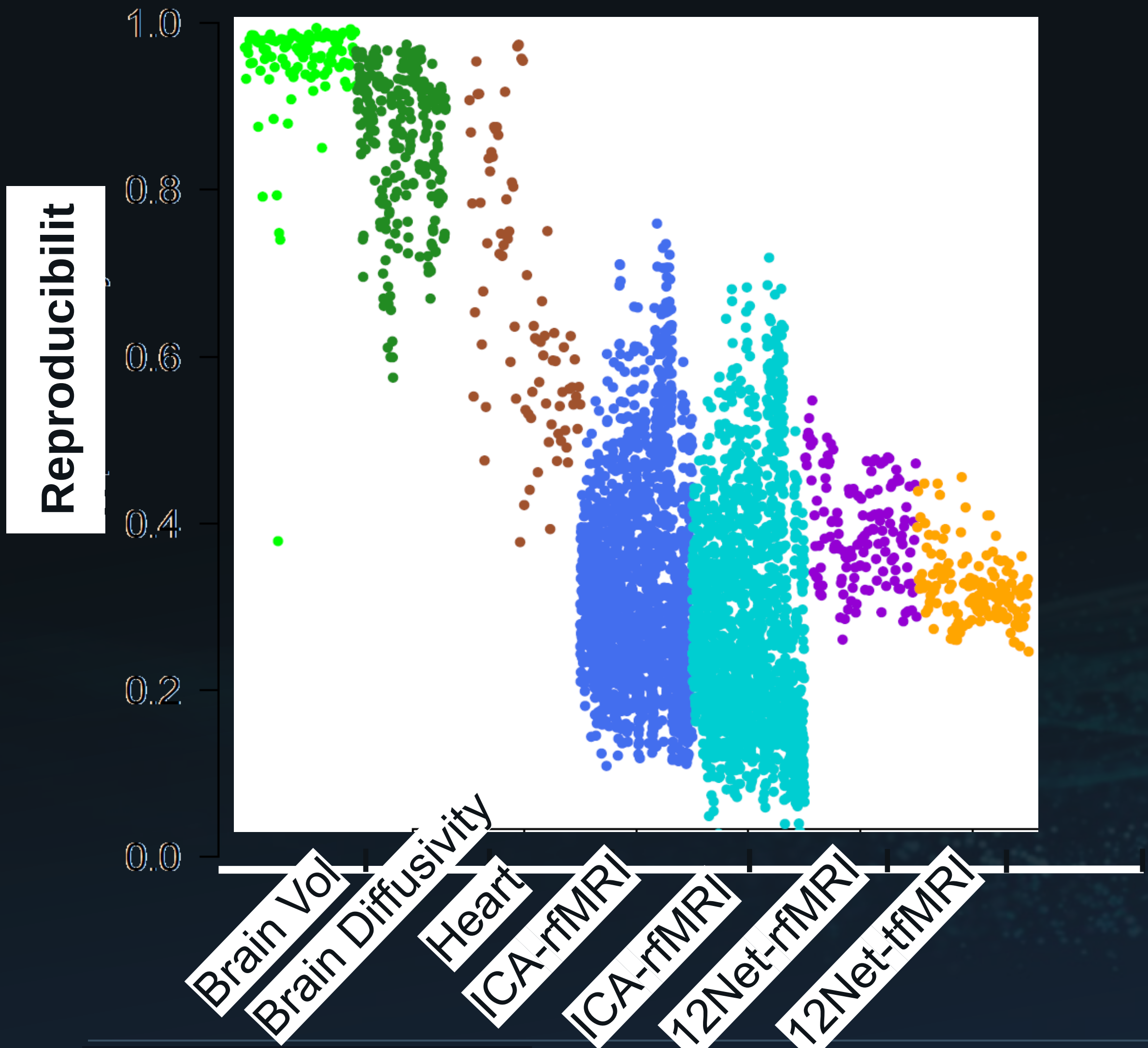
**For a heterogeneous, clinically defined disorder, the endophenotype (or imaging traits) is 'closer to the underlying biology,'**

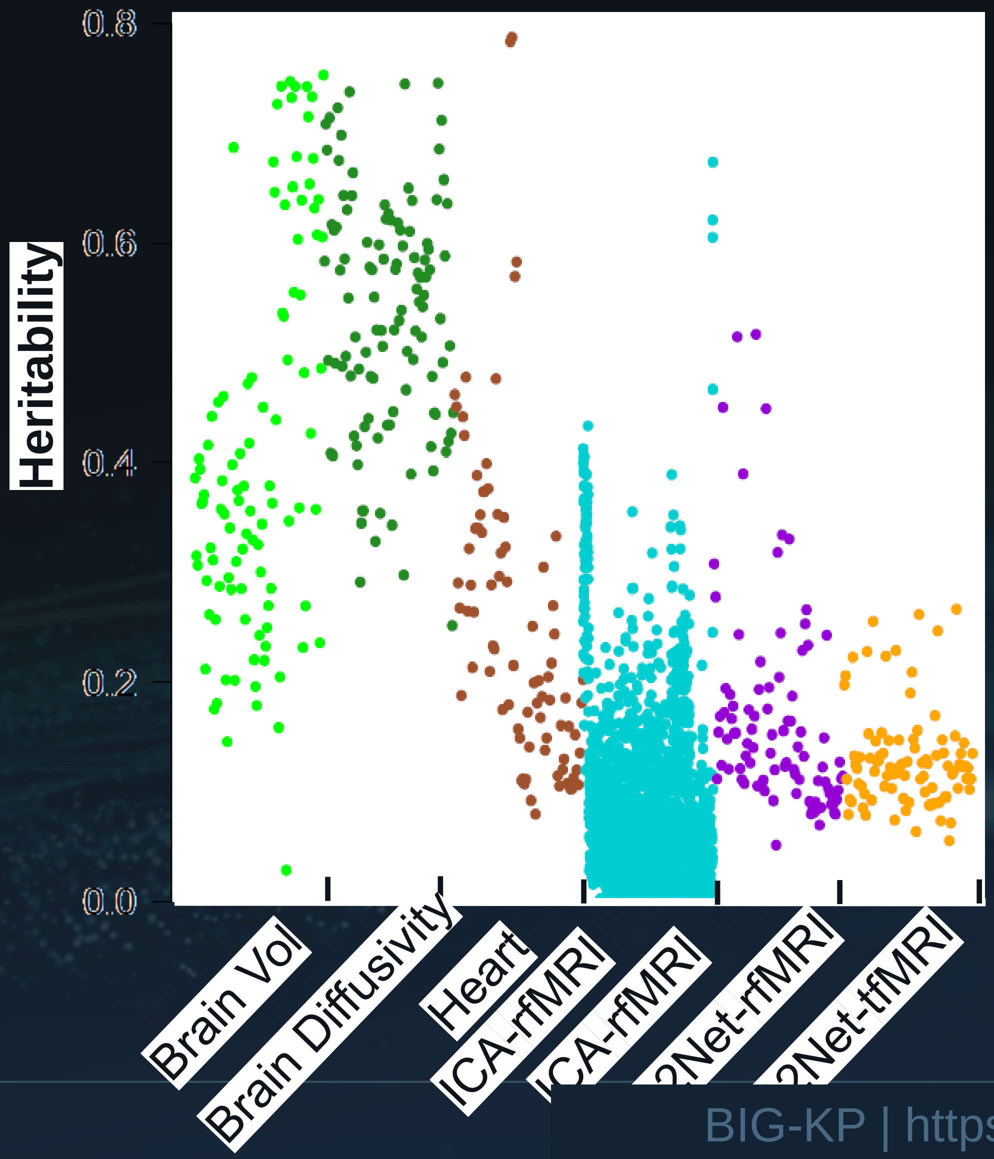
- **Be reproducible and heritable.**
- **Being informative about disorder risk.**
- **Providing mechanistic connections linking genetic variation to clinical measures.**
- **Some imaging traits (or brain circuits) may be treatable (e.g., ECT, TMS).**
- **Increasing the power of genetic search for** polygenic genetic architecture**.**



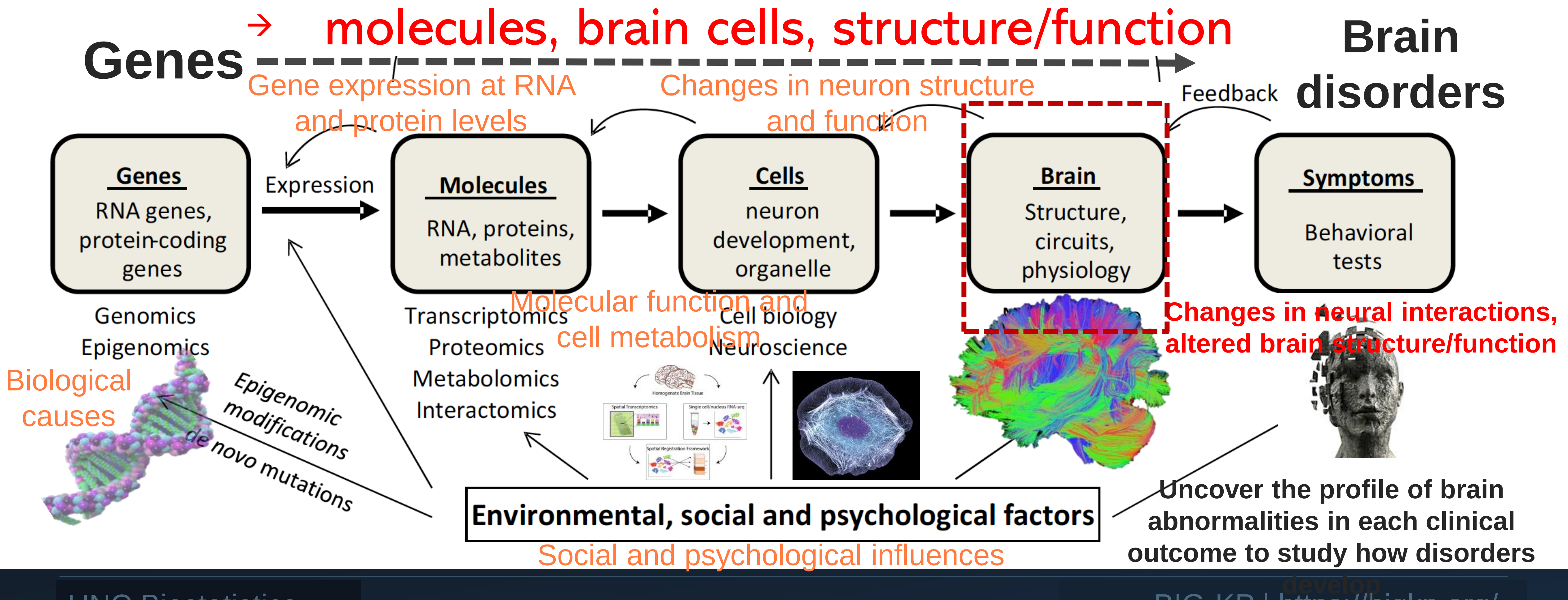
# IG: Reproducibility and Heritability



# Brain Imaging Genetics Paradigm

Neuroimaging: an important component to help understand the complex biological pathways of brain disorders

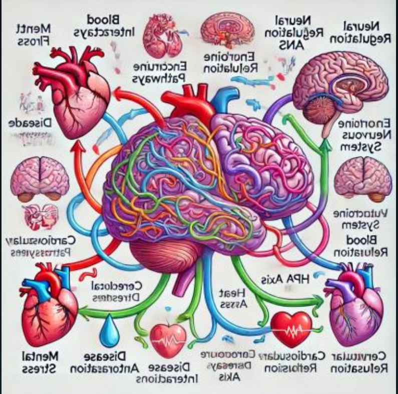


# Part II

## The Brain-Heart Axis

# The Brain-Heart Axis

**The brain-heart axis refers to the bidirectional communication between the brain and the heart, playing a crucial role in regulating physiological functions and maintaining overall health.**



## Neural Regulation:

- **Autonomic Nervous System (ANS):** regulate heart rate, blood pressure, and cardiac output.
- **Vagus Nerve:** reduce heart rate and promoting relaxation.

## Endocrine Pathways:

- **Hypothalamic-Pituitary-Adrenal (HPA) Axis:** Influences heart function through the release of hormones, affecting blood pressure and cardiovascular health.
- **Catecholamines:** Adrenaline and noradrenaline released during stress increase heart rate and cardiac output.

## Blood Flow and Oxygen Supply:

- **Cerebral Perfusion:** The heart ensures a continuous supply of oxygenated blood to the brain, essential for cognitive functions and neural health.
- **Cerebral Autoregulation:** Mechanisms that maintain stable blood flow to the brain despite changes in systemic blood pressure.

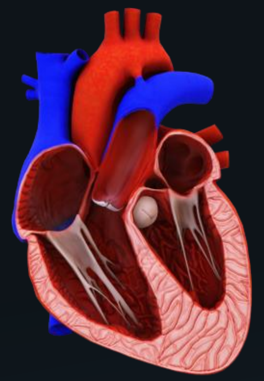
# The Brain-Heart Axis

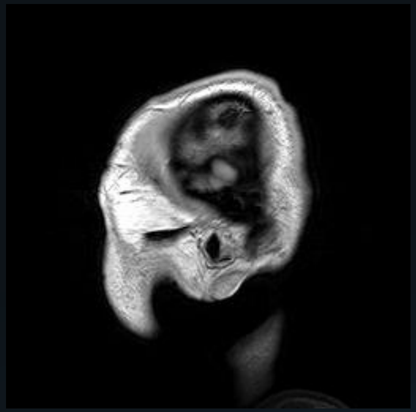
## Disease Interactions:

- **Cardiovascular Diseases:** Conditions like atrial fibrillation and heart failure are linked to brain diseases such as stroke, dementia, and cognitive impairment due to reduced cerebral perfusion.
- **Mental Disorders:** Mental illnesses, including schizophrenia, bipolar disorder, epilepsy, and depression, increase the risk of CVD.

## Acute Mental Stress:

- **Impact on Cardiovascular Health:** Acute stress can cause vascular inflammation and increase the risk of atherosclerosis due to stress-induced leukocyte migration.



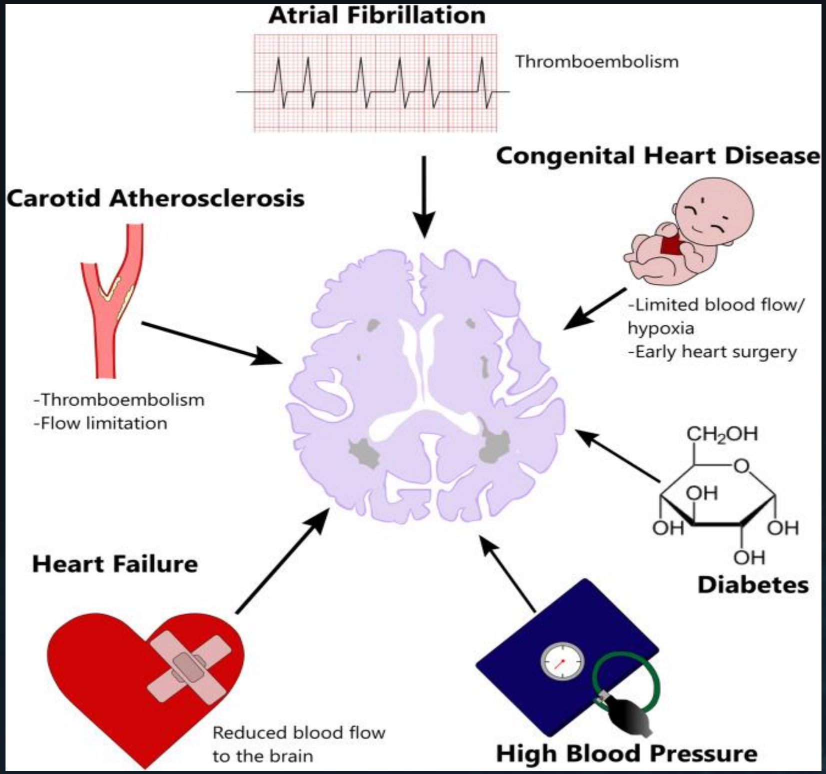


## Research Significance:

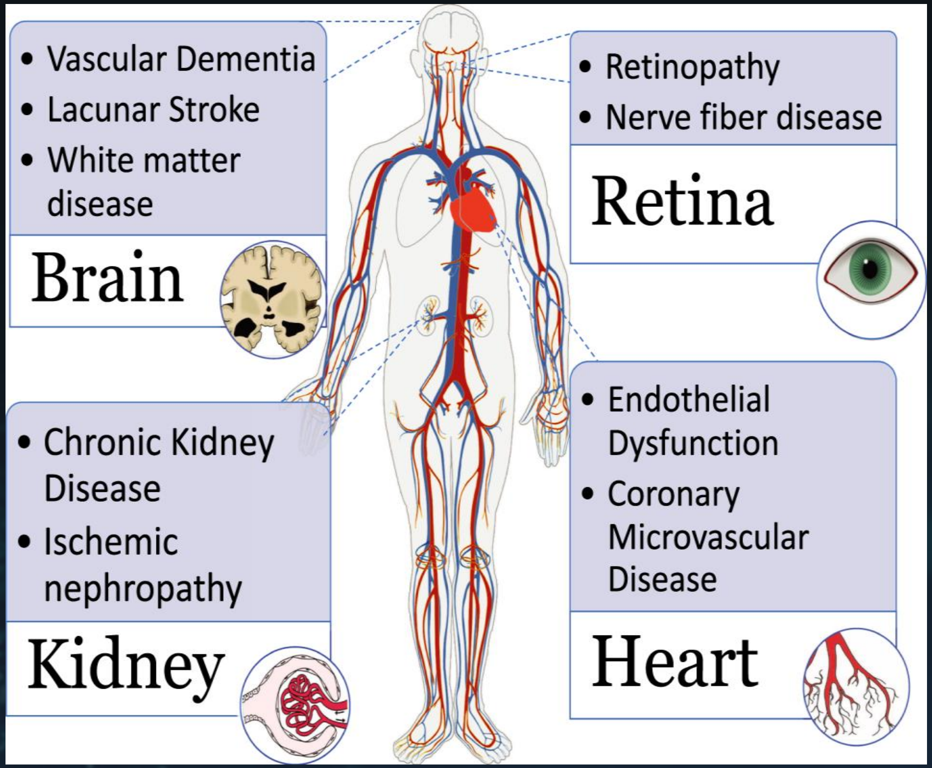
- **Integrated Treatment Approaches:** Lead to better treatments for neurocardiological disorders.
- **Comprehensive Studies:** A need for larger studies to provide a complete picture of the structural and functional links between heart and brain health.

# Cardiovascular Disease & Brain Health

## (Neuro)imaging: help understand the complex interplay between brain and other human organs and their underlying genetic overlaps



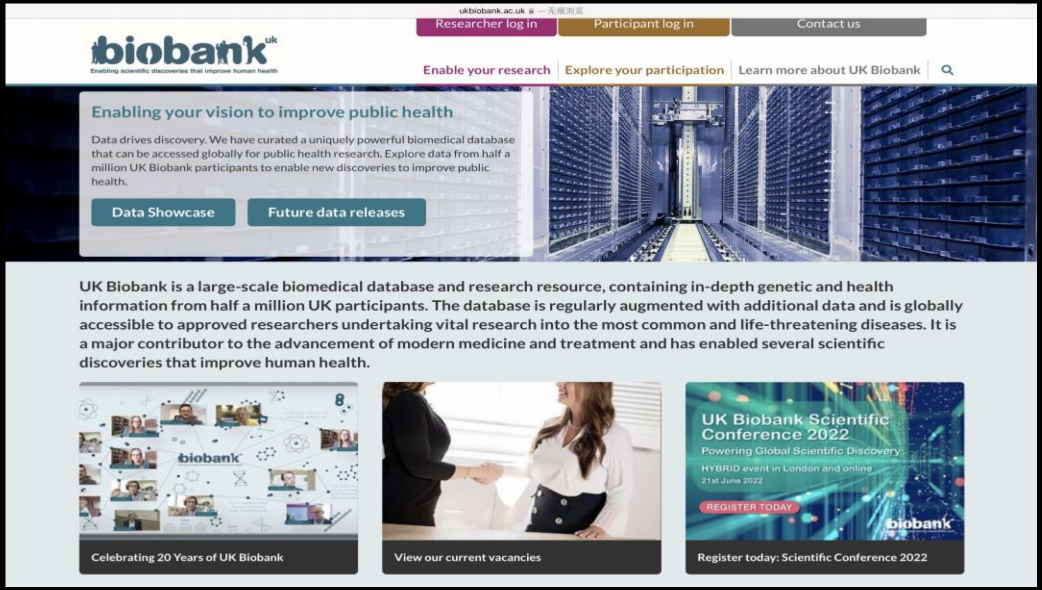

Possible causal factors of brain structure changes, resulting in brain disorders like stroke, dementia and cognitive impairment



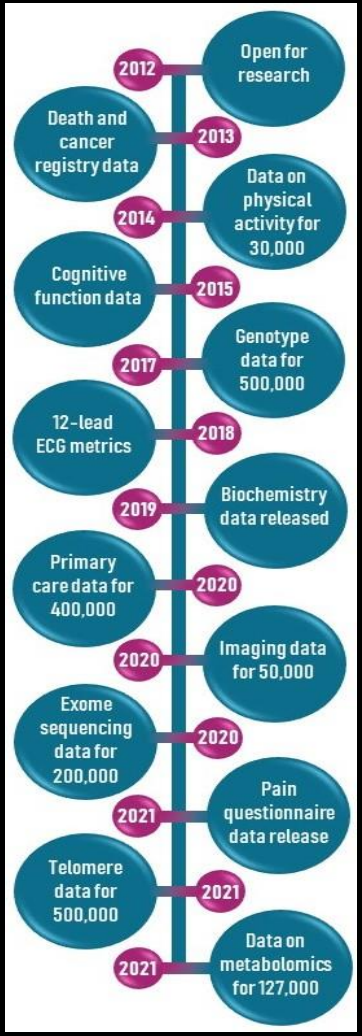

Many diseases (e.g., microvascular disease, high blood pressure) are multisystem disorders

# The UK Biobank Study

UK Biobank has collected and continues to collect extensive environmental, lifestyle, and genetic data on half a million participants.




**2006-now**

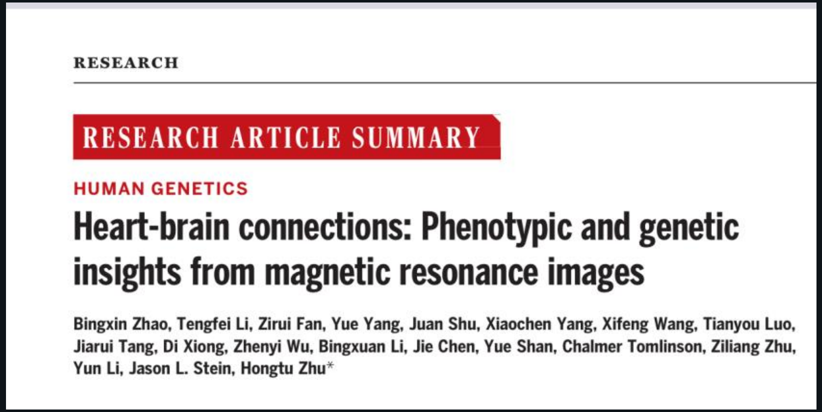



- **Imaging:** Brain, heart and full body MR imaging, plus full body DEXA scan of the bones and joints and an ultrasound of the carotid arteries. The goal is to image 100,000 participants, and to invite participants back for a repeat scan some years later.
- **Genetics:** Genotyping, whole exome sequencing & whole genome sequencing for all participants.
- **Health linkages:** Linkage to a wide range of electronic health-related records, including death, cancer, hospital admissions and primary care records.
- **Biomarkers:** Data on more than 30 key biochemistry markers from all participants, taken from samples collected at recruitment and the first repeat assessment.
- **Activity monitor:** Physical activity data over a 7-day period collected via a wrist-worn activity monitor for 100,000 participants plus a seasonal follow-up on a subset.
- **Online questionnaires:** Data on a range of exposures and health outcomes that are difficult to assess via routine health records, including diet, food preferences, work history, pain, cognitive function, digestive health and mental health.
- **Repeat baseline assessments:** A full baseline assessment is undertaken during the imaging assessment of 100,000 participants.
- **Samples:** Blood & urine was collected from all participants, and saliva for 100,000.

# Part III

## Genetic Architecture of the Brain-Heart Connection

# Overview

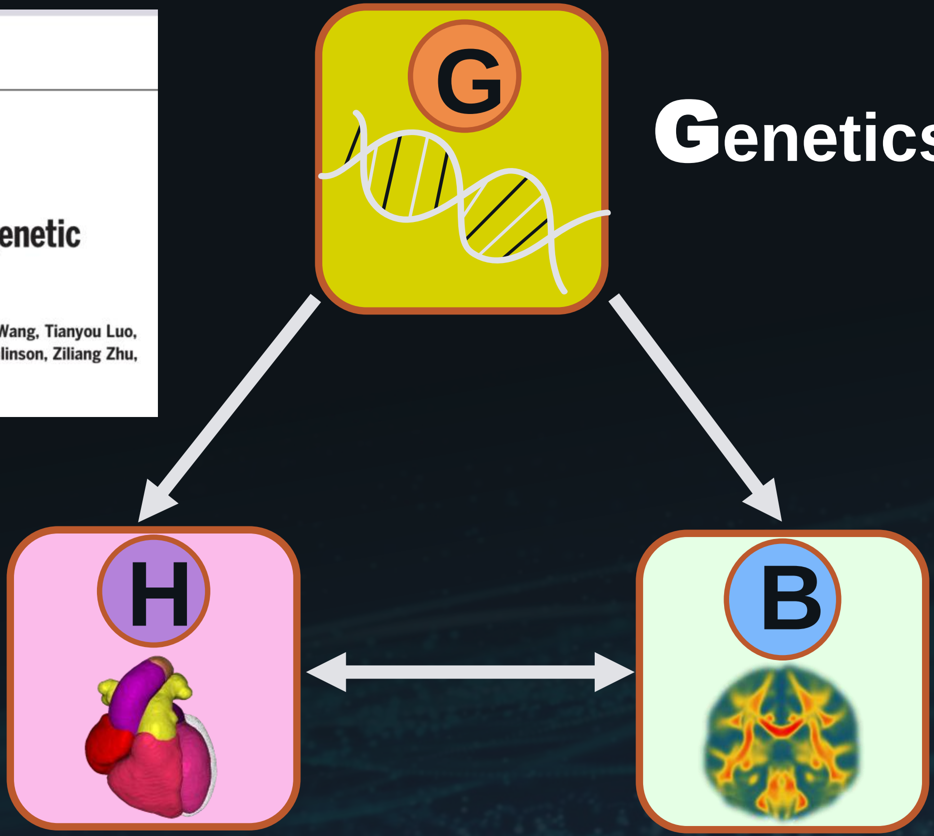

RESEARCH

RESEARCH ARTICLE SUMMARY

HUMAN GENETICS

Heart-brain connections: Phenotypic and genetic insights from magnetic resonance images

Bingxin Zhao, Tengfei Li, Zirui Fan, Yue Yang, Juan Shu, Xiaochen Yang, Xifeng Wang, Tianyou Luo, Jiarui Tang, Di Xiong, Zhenyi Wu, Bingxuan Li, Jie Chen, Yue Shan, Chalmer Tomlinson, Ziliang Zhu, Yun Li, Jason L. Stein, Hongtu Zhu*




**Genetics**

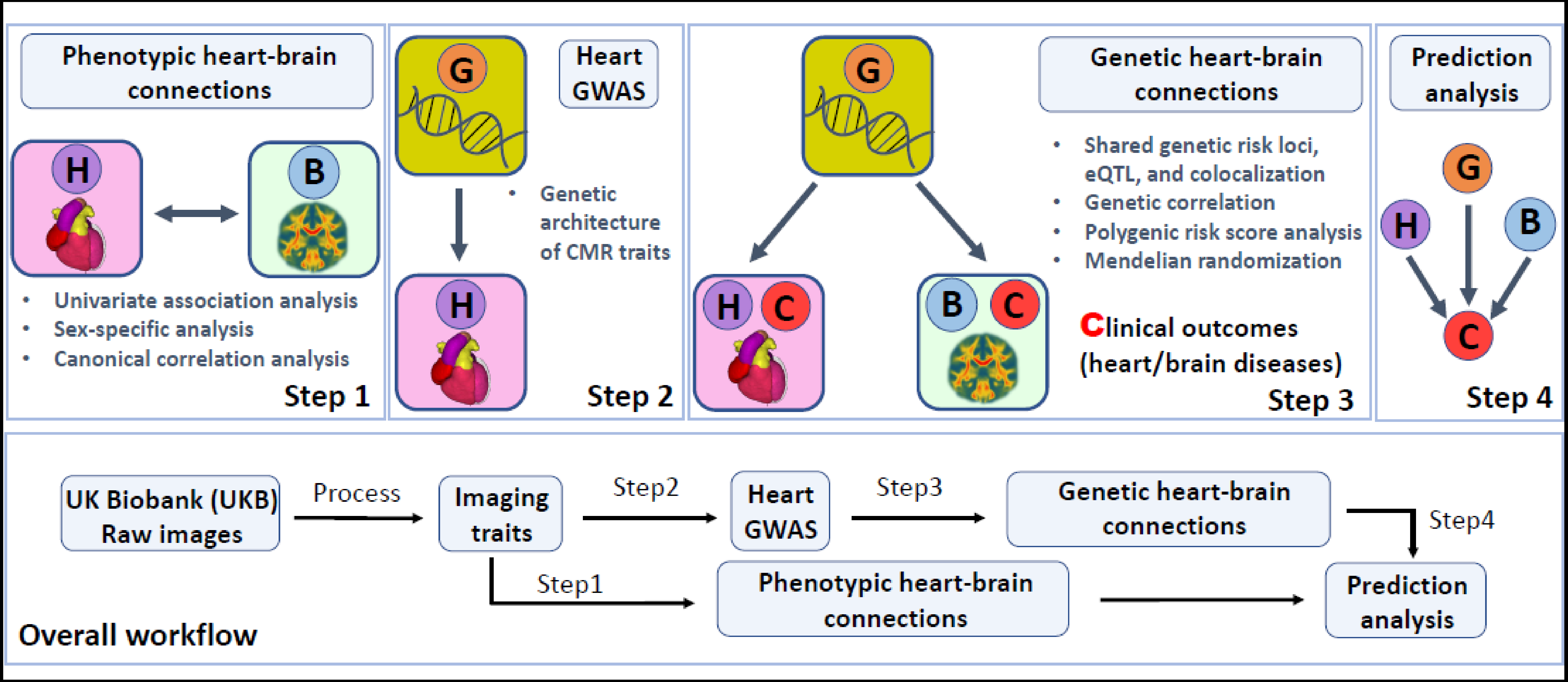
Left ventricle
Right ventricle
Left atrium
Right atrium
Ascending aorta
Descending aorta

Structural MRI
Diffusion MRI
Resting functional MRI
Task functional MRI

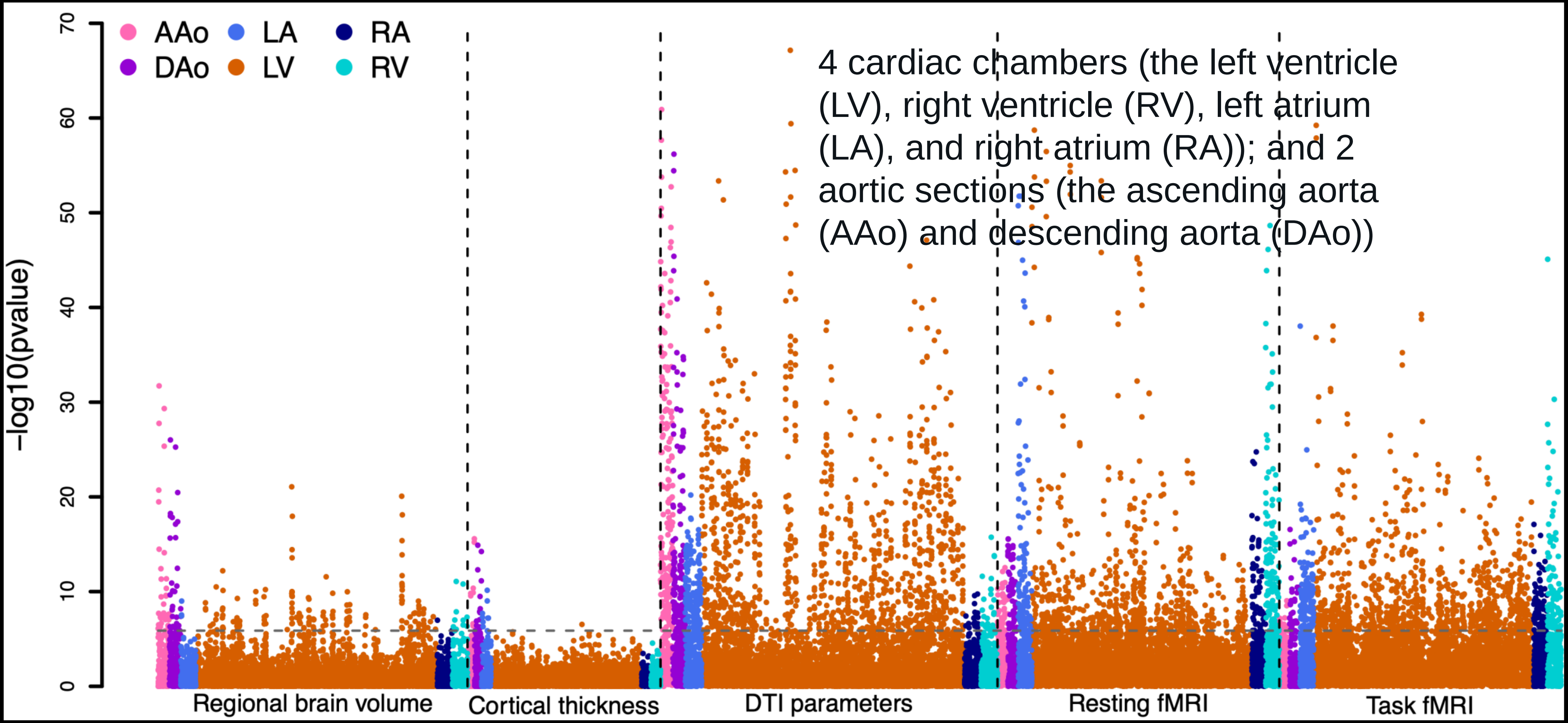
**Heart health**
(measured by CMR)

**Brain health**
(measured by brain MRI)

# Overview

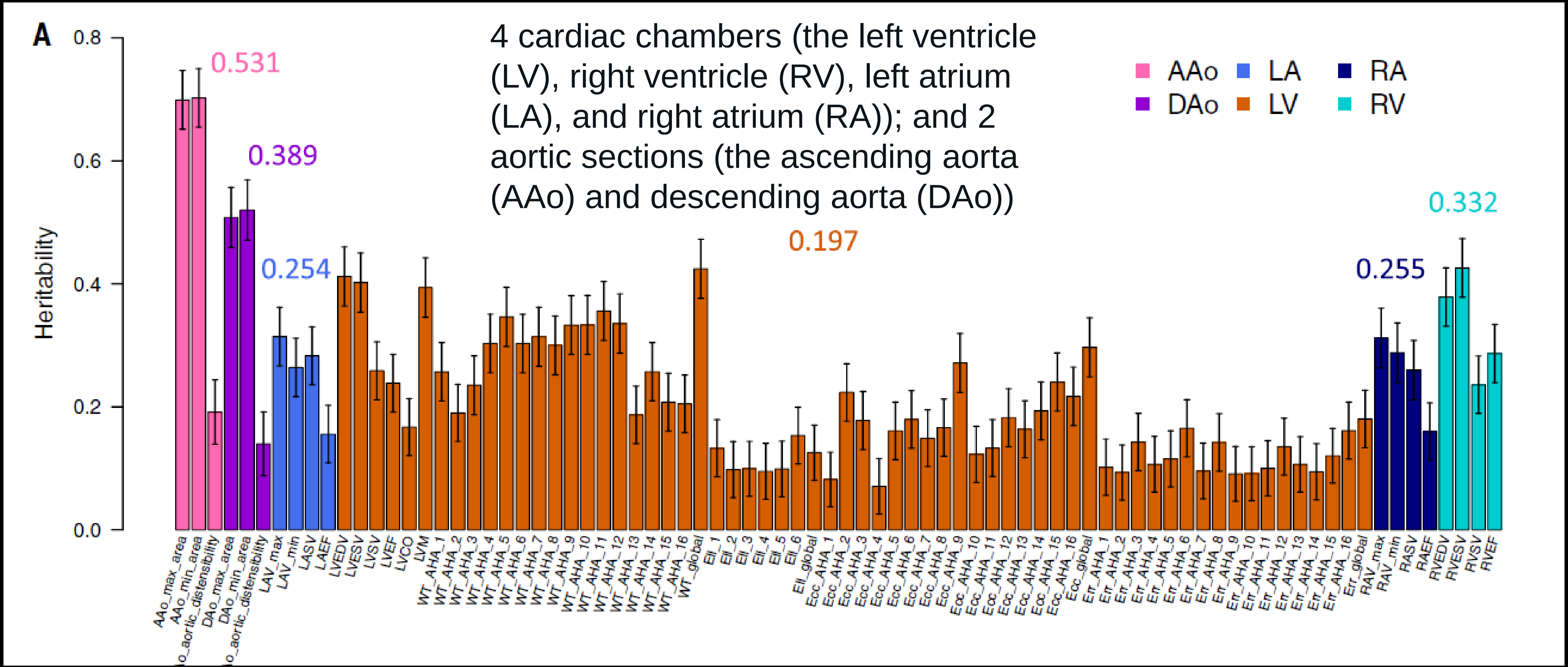

Phenotypic heart-brain connections
H
B
Univariate association analysis
Sex-specific analysis
Canonical correlation analysis
Step 1
G
Heart GWAS
Genetic architecture of CMR traits
H
Step 2
G
Genetic heart-brain connections
Shared genetic risk loci, eQTL, and colocalization
Genetic correlation
Polygenic risk score analysis
Mendelian randomization
H C
B C
Clinical outcomes (heart/brain diseases)
Step 3
Prediction analysis
G
H
B
C
Step 4
UK Biobank (UKB) Raw images
Process
Imaging traits
Step2
Heart GWAS
Step3
Genetic heart-brain connections
Step4
Step1
Phenotypic heart-brain connections
Prediction analysis
Overall workflow

# Phenotypic Heart-Brain Connections

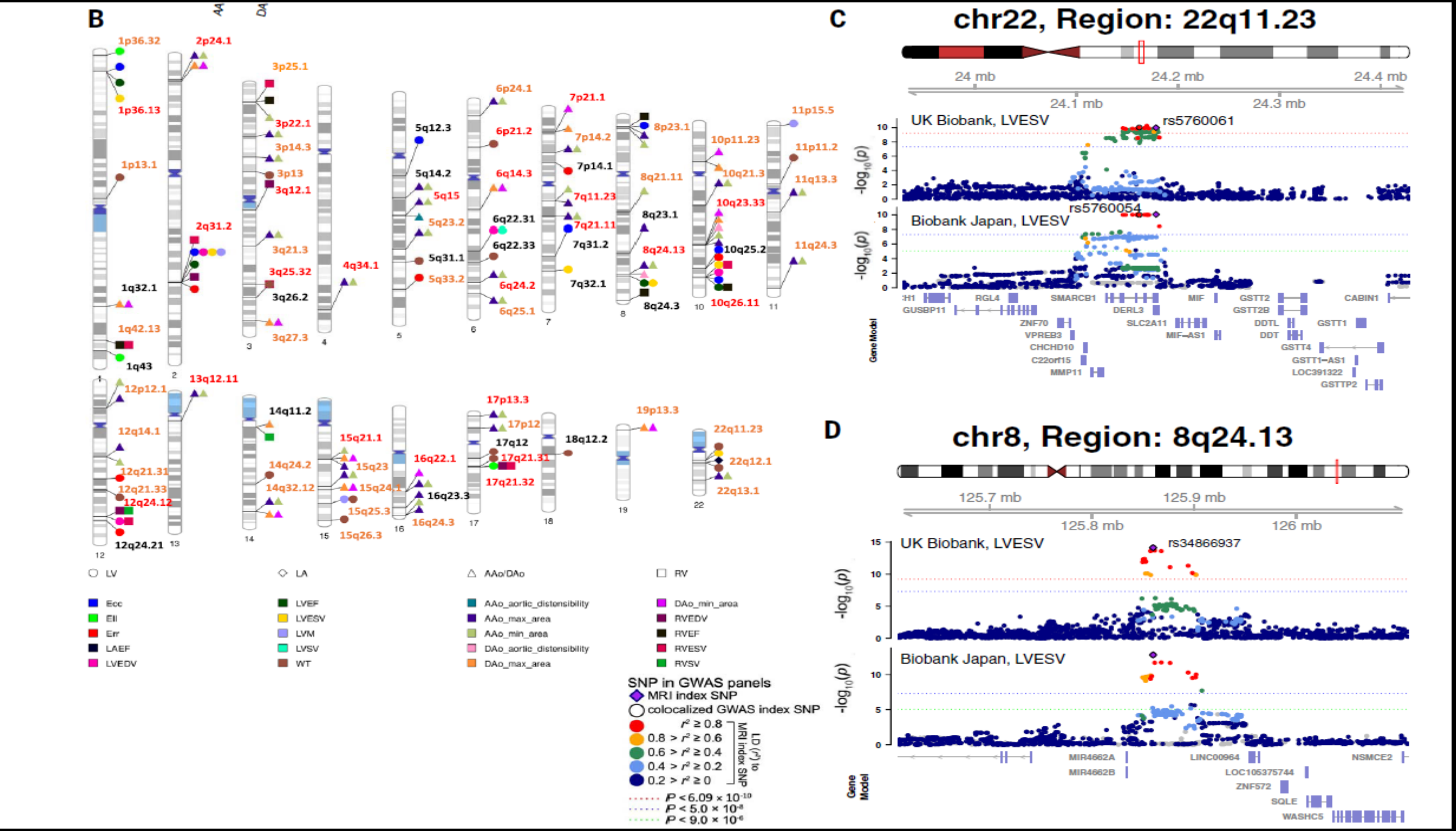



4 cardiac chambers (the left ventricle (LV), right ventricle (RV), left atrium (LA), and right atrium (RA)); and 2 aortic sections (the ascending aorta (AAo) and descending aorta (DAo))

# SNP heritability of 82 CMR traits



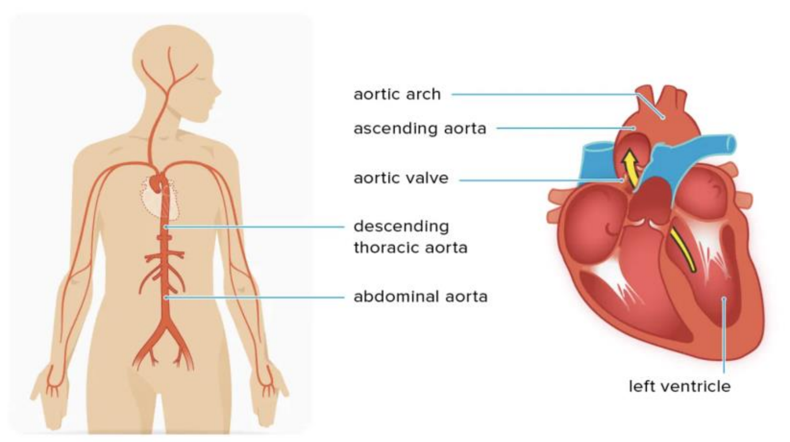
# Genetics of CMR traits in the UKB



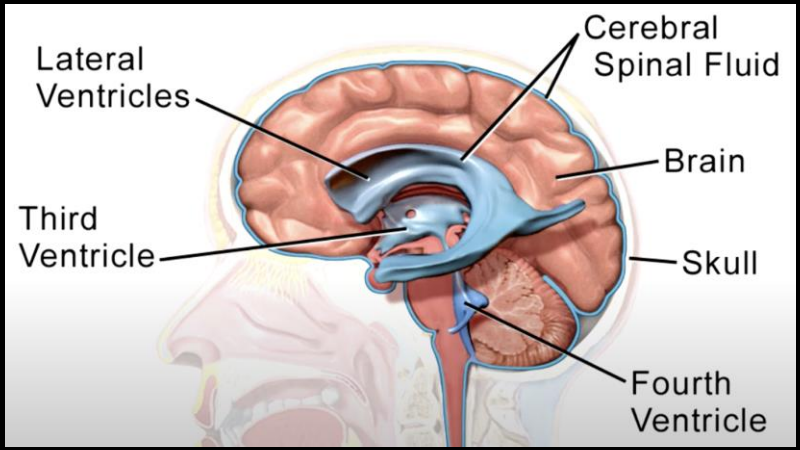

Ideogram of 80 genomic regions associated with CMR traits

LV end-systolic volume (LVESV)

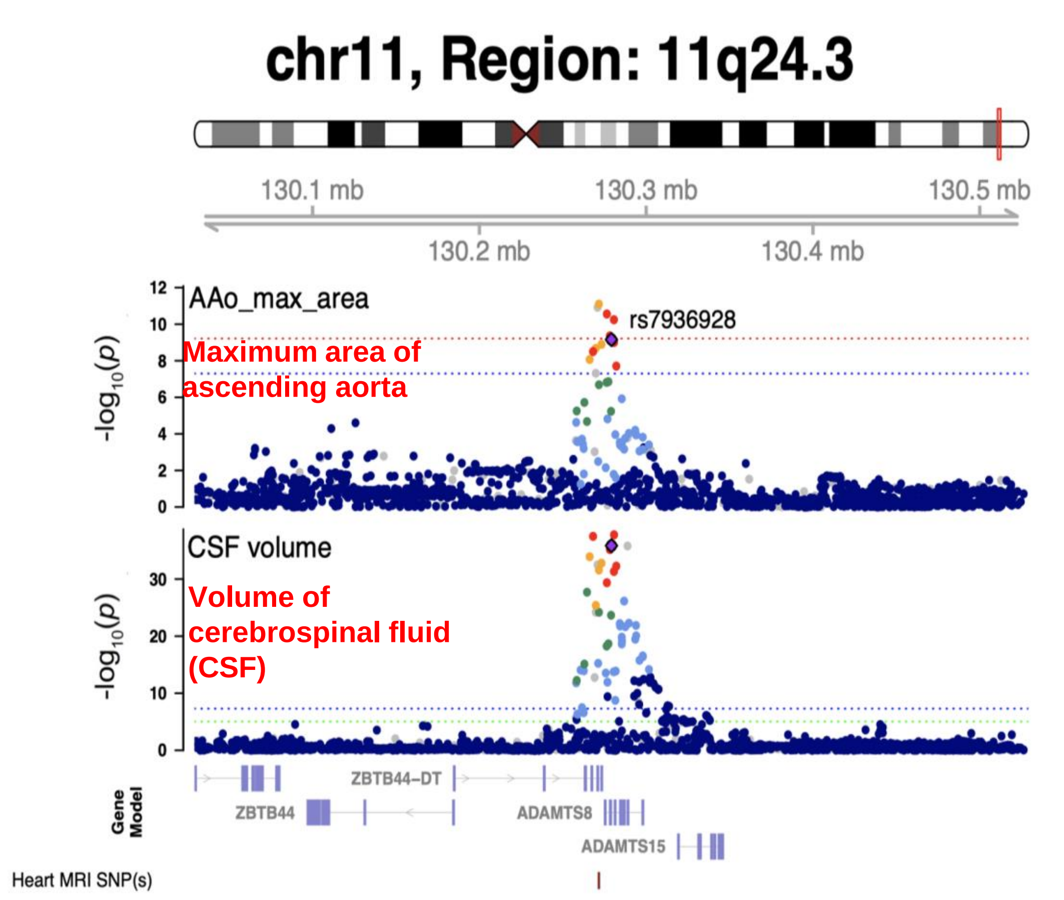
# Selected genetic loci



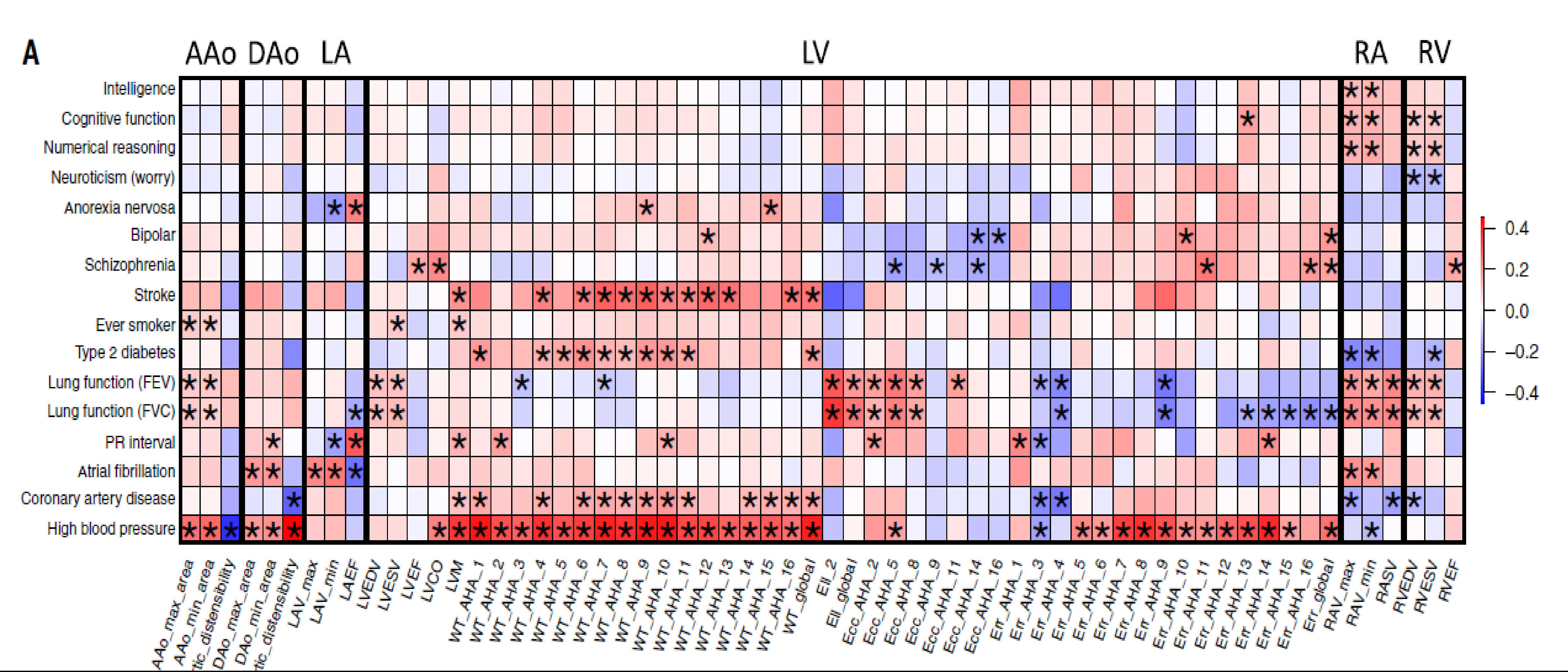

Heart MRI




Brain MRI



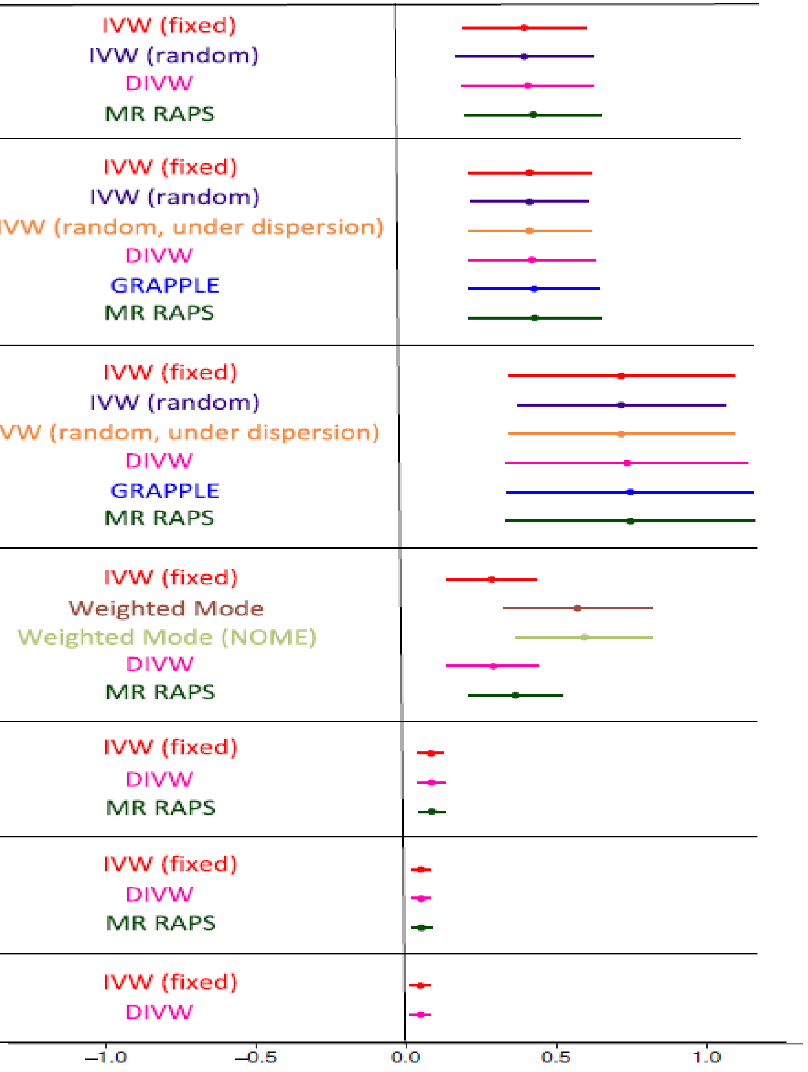
# Genetic Correlations



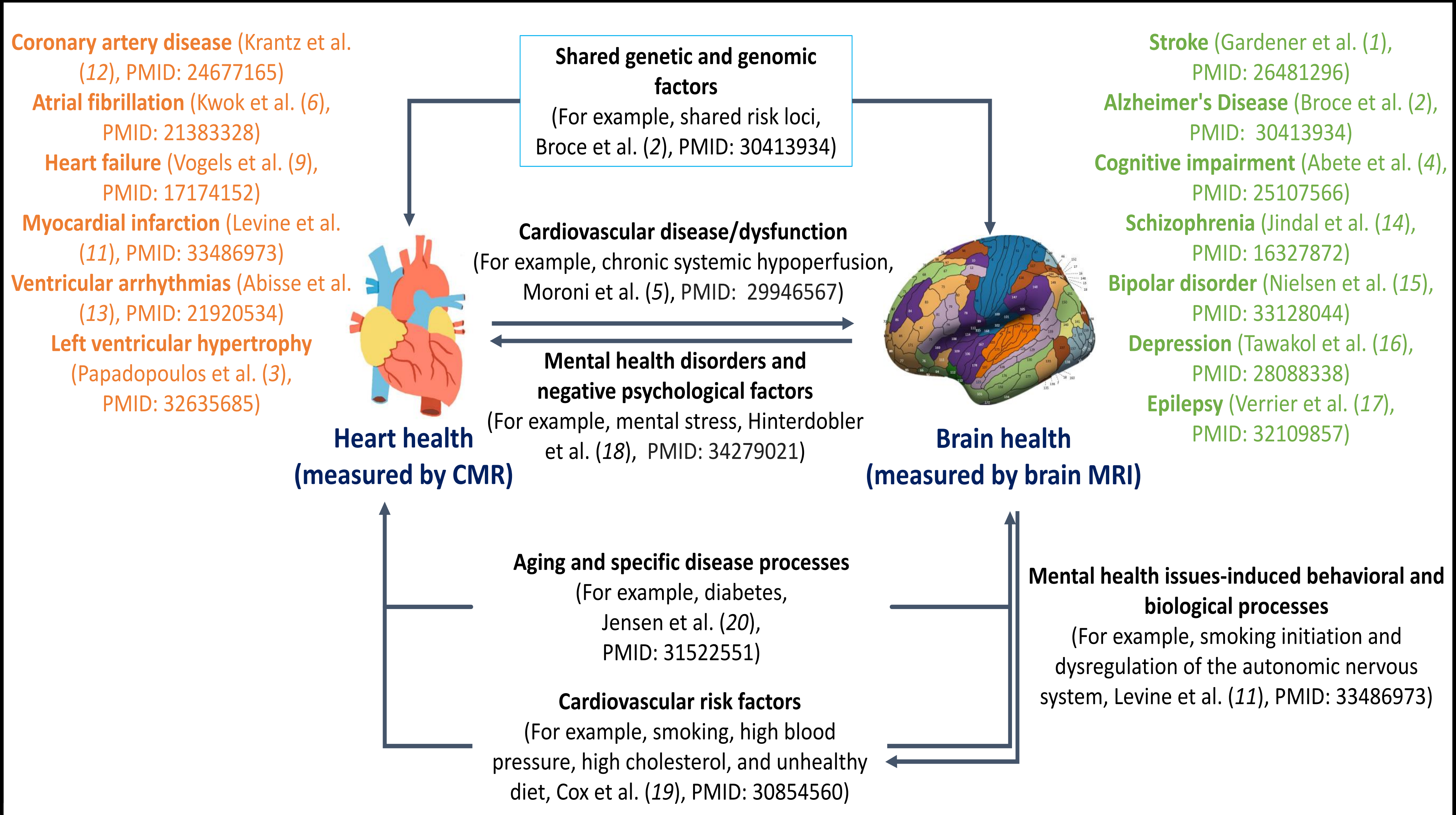
# MR: Causal heart-brain relationships

| Exposure | Category | Outcome | #IVs | Method |
|---|---|---|---|---|
| WT AHA 9 | LV | Bipolar disorder | 7 | IVW (fixed) |
| | | | | IVW (random) |
| | | | | DIVW |
| | | | | MR RAPS |
| LVESV | LV | Cross disorders | 12 | IVW (fixed) |
| | | | | IVW (random) |
| | | | | IVW (random, under dispersion) |
| | | | | DIVW |
| | | | | GRAPPLE |
| | | | | MR RAPS |
| WT AHA 12 | LV | Cross disorders | 6 | IVW (fixed) |
| | | | | IVW (random) |
| | | | | IVW (random, under dispersion) |
| | | | | DIVW |
| | | | | GRAPPLE |
| | | | | MR RAPS |
| AAo min area | AAo | Cross disorders | 34 | IVW (fixed) |
| | | | | Weighted Mode |
| | | | | Weighted Mode (NOME) |
| | | | | DIVW |
| | | | | MR RAPS |
| WT AHA 11 | LV | Depression | 7 | IVW (fixed) |
| | | | | DIVW |
| | | | | MR RAPS |
| AAo max area | AAo | Psychiatric diseases (FinnGen) | 47 | IVW (fixed) |
| | | | | DIVW |
| | | | | MR RAPS |
| AAo min area | AAo | Psychiatric diseases (FinnGen) | 50 | IVW (fixed) |
| | | | | DIVW |

Coefficient



# Potential heart-brain relationships

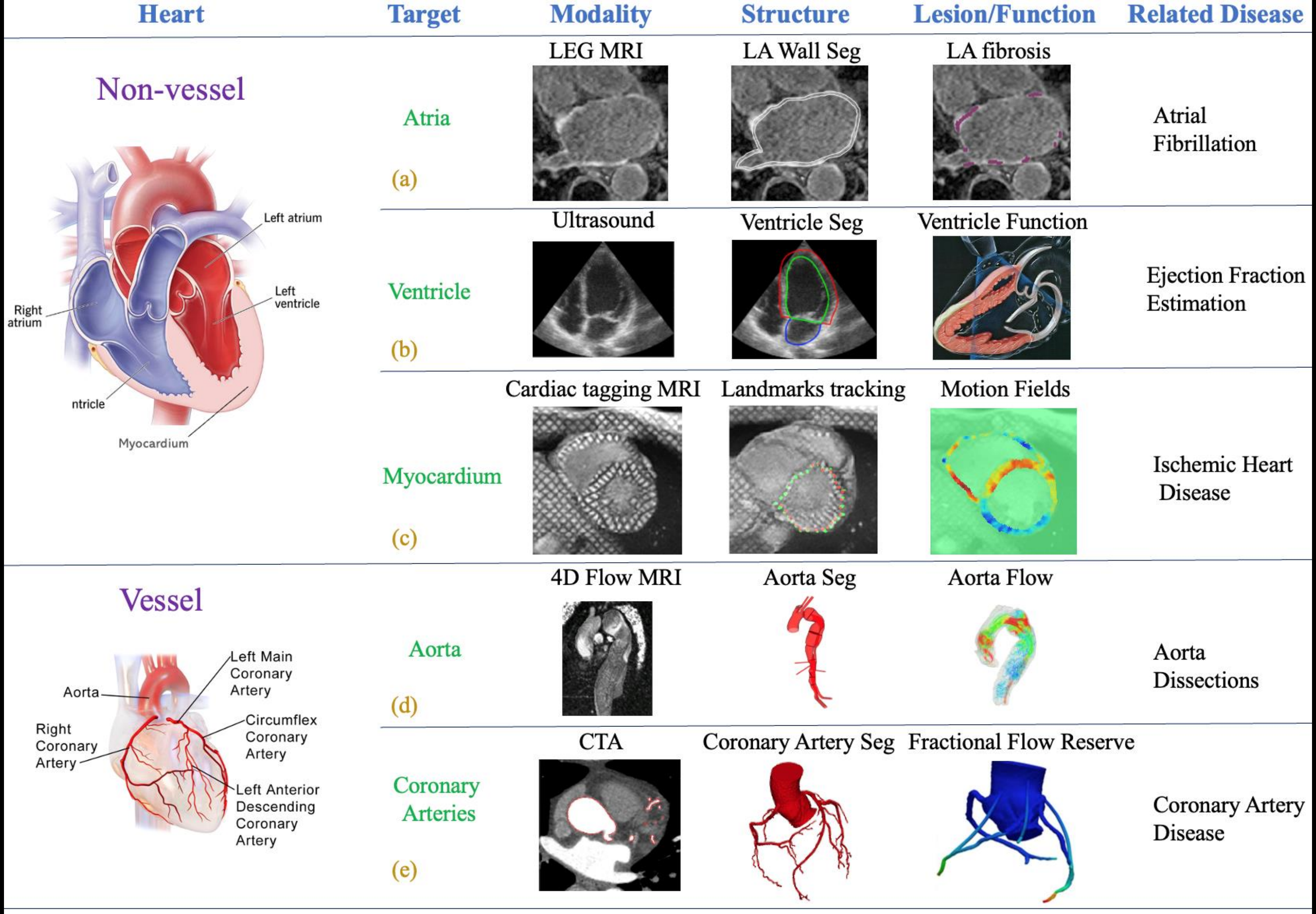


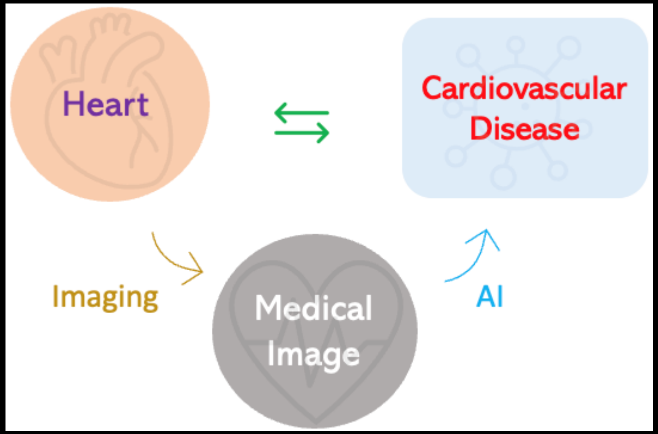
# Part IV

## Artificial Intelligence in Image-based Cardiovascular Disease Analysis

# Cardiovascular Diseases (CVD)

CVDs and anatomical structures involved and their functions

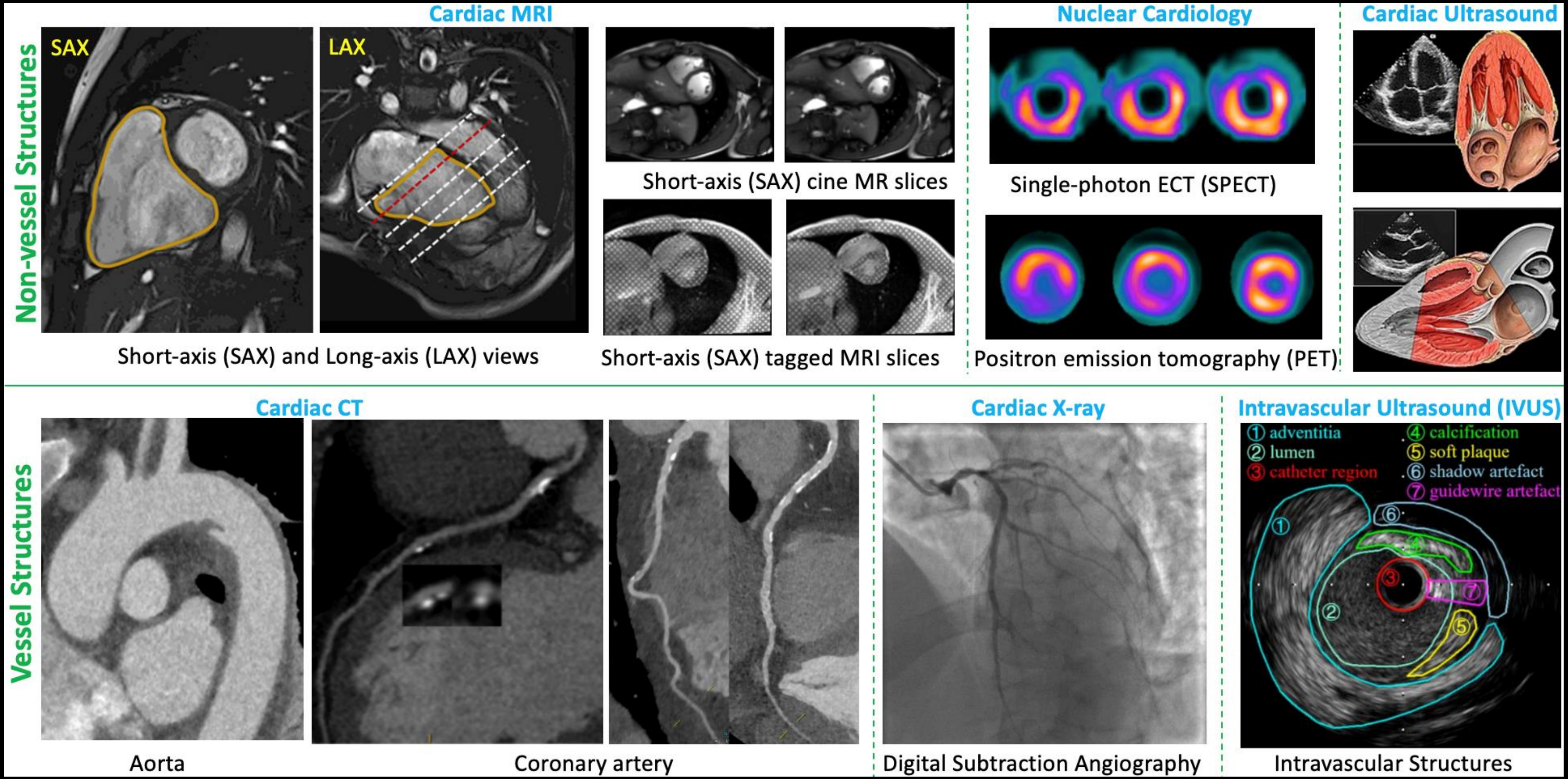



Wang, X. and Zhu, H (2024). Artificial Intelligence in Image-based Cardiovascular Disease Analysis: A Comprehensive Survey and Future Outlook

# Cardiac Imaging

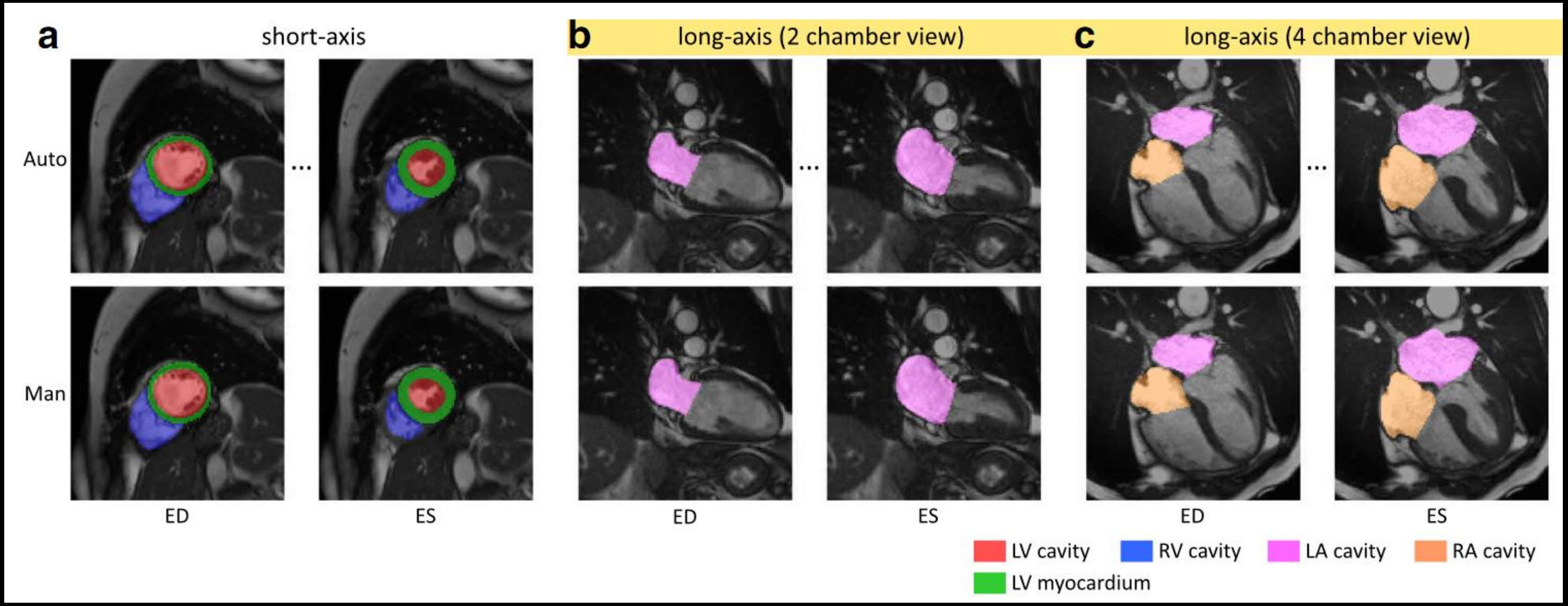
**Commonly employed modalities in cardiac imaging**

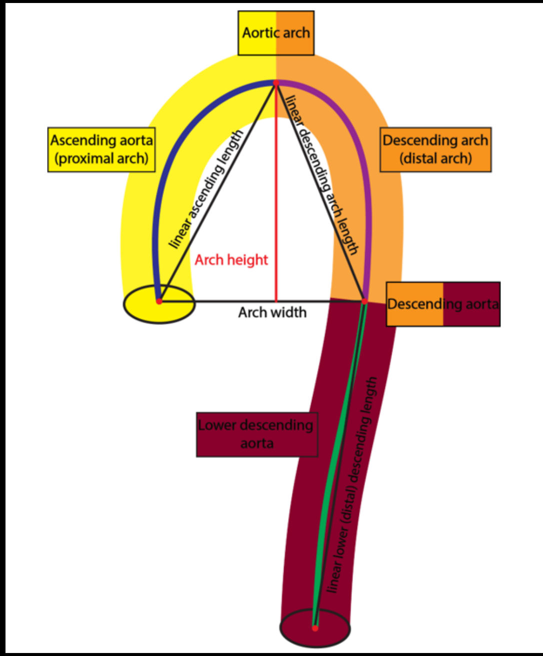





**Categorize according to anatomical structures**

# Cardiovascular Features: Structural




**Left/Right Ventricle:**

- End-diastolic Volume
- End-systolic Volume
- Myocardial Thickness/Mass
- Stroke Volume
- Ejection Fraction
- Cardiac Output

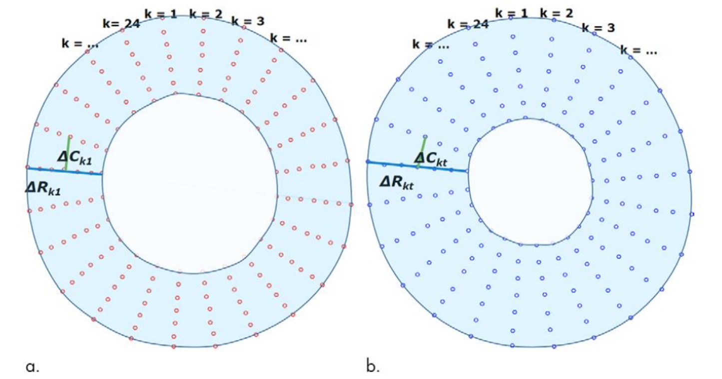
**Left/Right Atrium:**

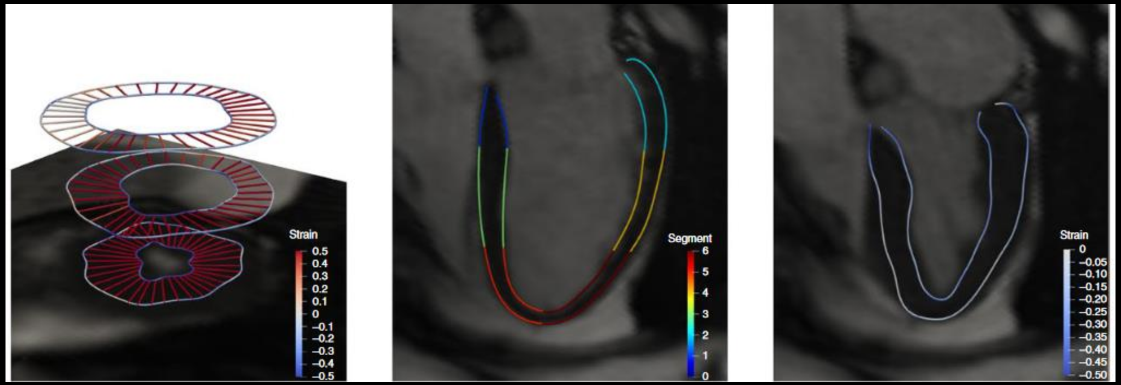
- Maximum Volume
- Minimum Volume
- Pre-contraction Volume
- Stroke Volume
- Ejection Fraction

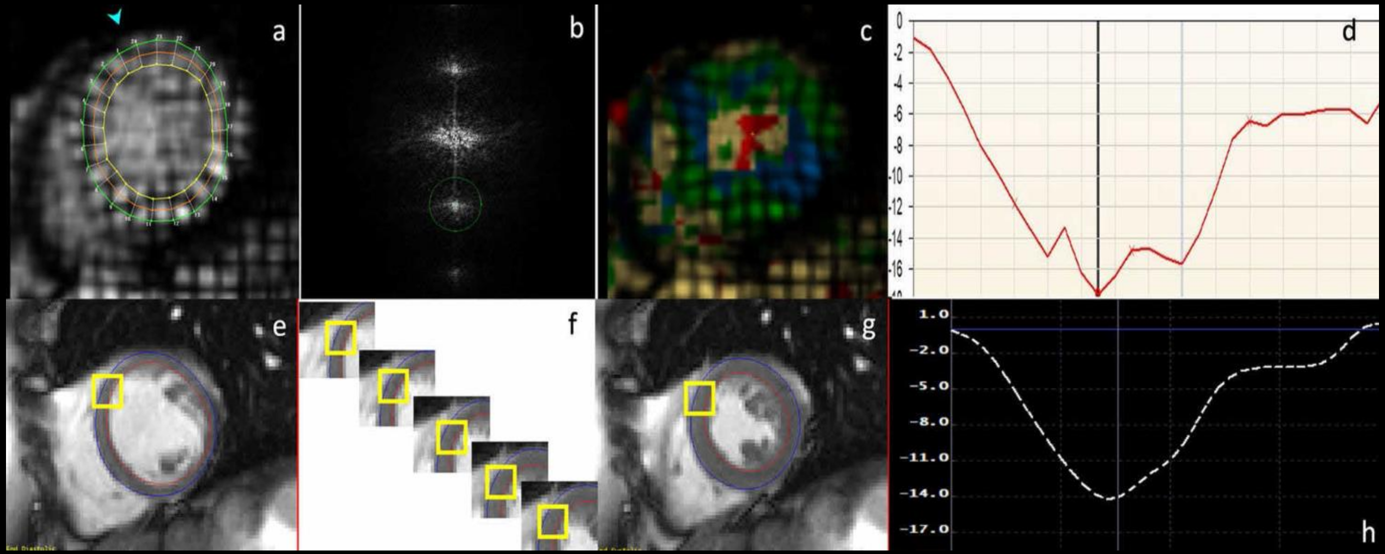
**Ascending/Descending Aorta:**

- Maximum/Minimum Diameter
- Maximum/Minimum Area
- Arch Width/Height
- Distensibility
- Tortuosity
- Curvature

# Cardiovascular Features: Functional




**Global/Regional Strain/Strain Rate(SR):**

- **Circumferential**
- **Radial**
- **Longitudinal**

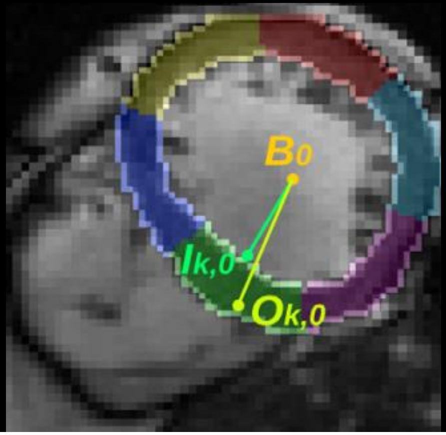


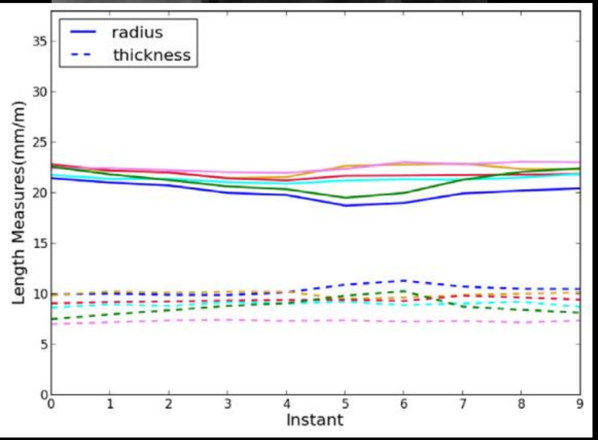
**Harmonic phase(HARP) on tagged CMR images**

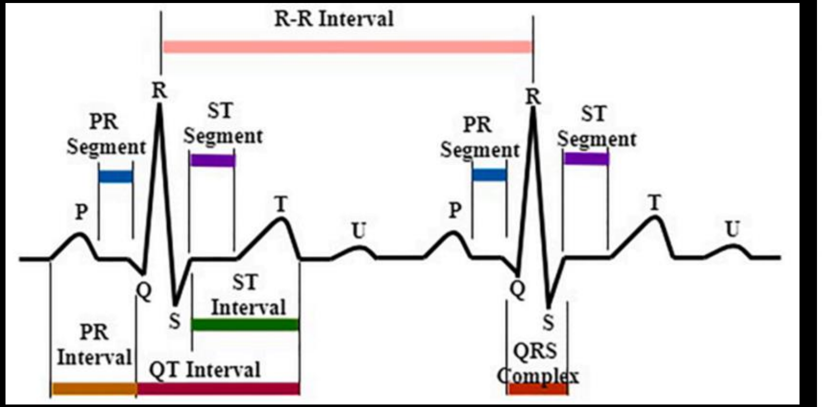
**Feature tracking(FT) on cine CMR images**

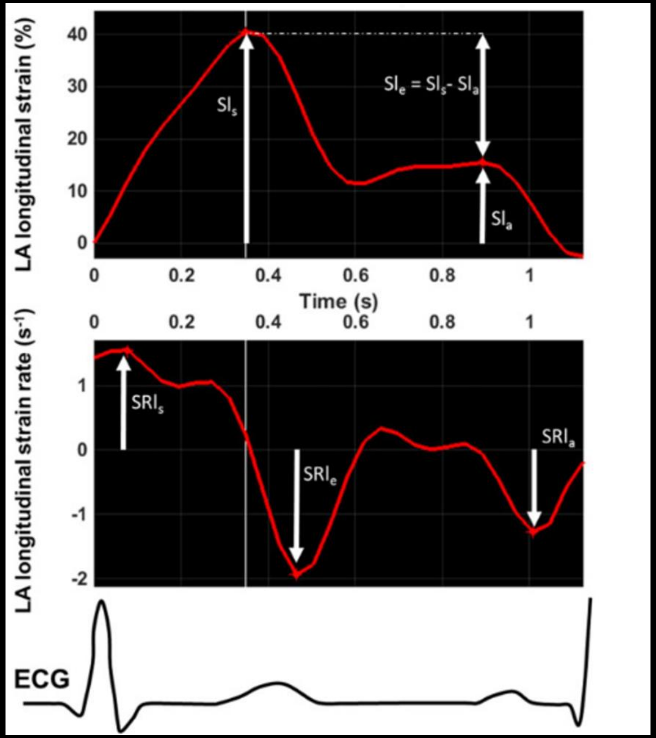
# Cardiovascular Features: Comprehensive

**Intricate features can be extracted through time series, information from electrocardiogram (ECG) , etc.**



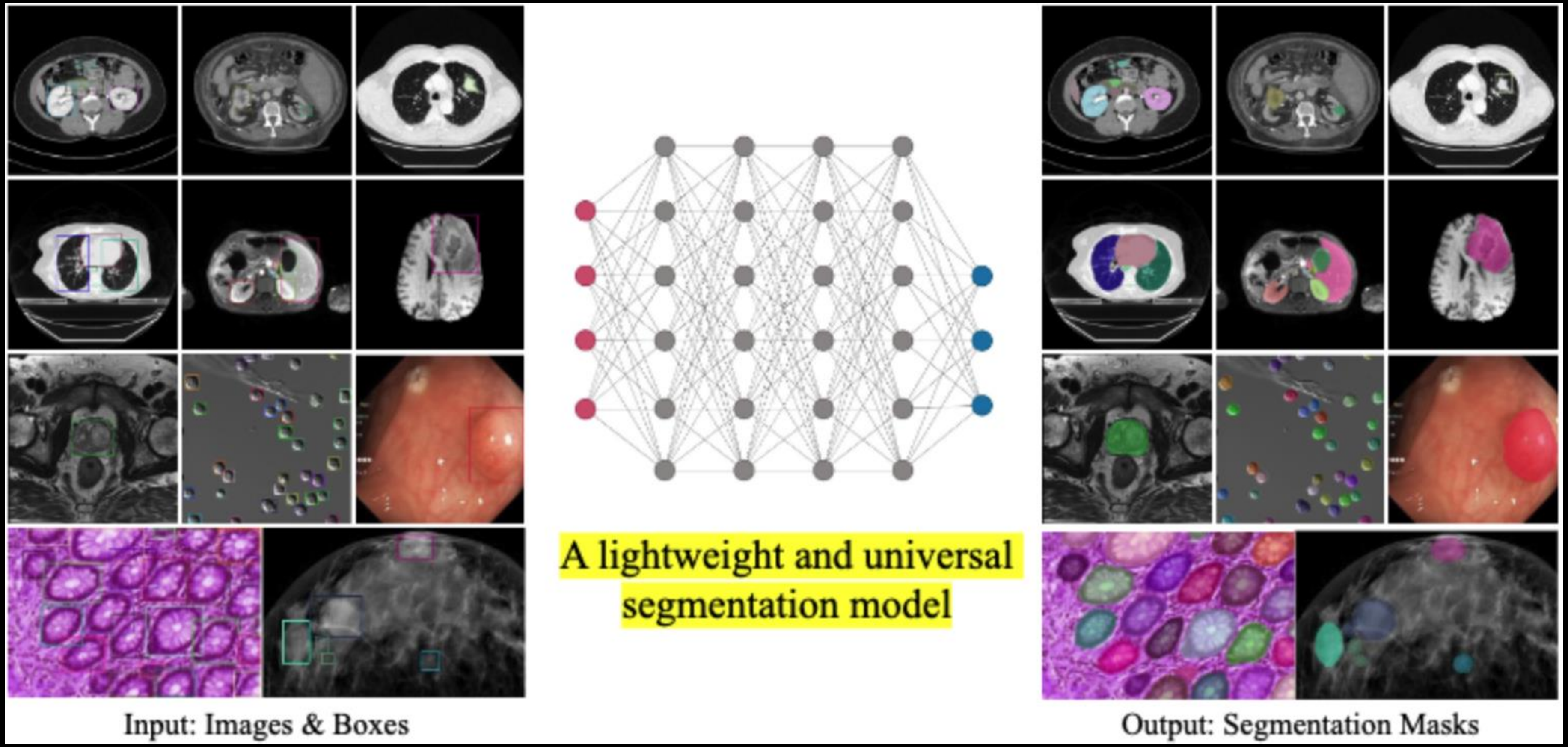




- **Radius motion disparity**
- **Thickness motion disparity**

- **Volume at different phases**
- **Derivative of volume: Peak filling/emptying rate**
- **Strain/Strain Rate at different phases**
- **Time/Frequency/Nonlinear ECG Features**

# AI foundation Model for Segmentation

CVPR 2024: SEGMENT ANYTHING IN MEDICAL IMAGES ON LAPTOP

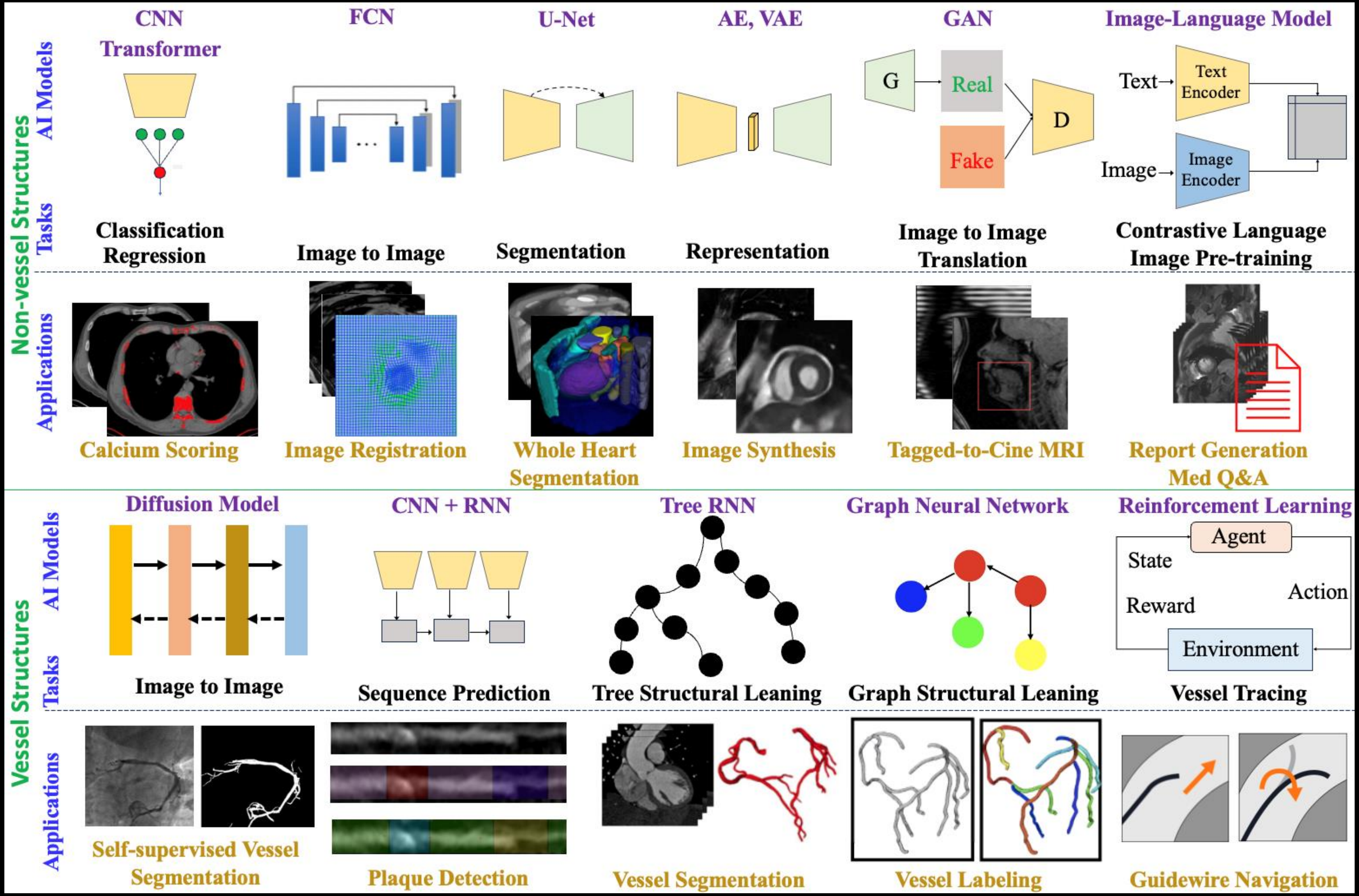



- Lightweight bounding box-based segmentation model
- Large-scale training dataset with 1,000,000+ image-mask pairs, covering 10 medical image modalities and more than 20 cancer types

Universal promptable medical image segmentation models that are deployable on laptops or other edge devices without reliance on GPUs

# AI for CVD Analysis

Examples of recent representative AI models for CVD Analysis

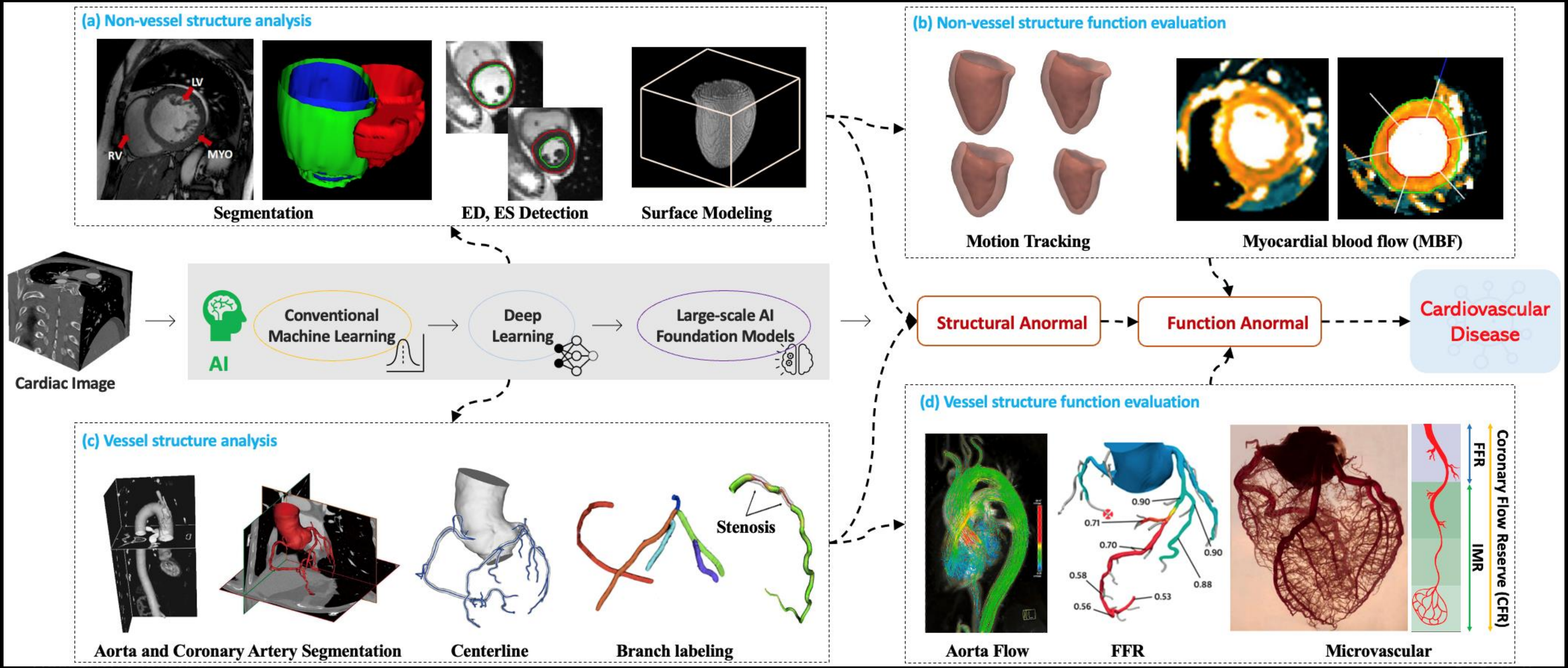



AI Methods for
Non-vessel Tasks

AI Methods for
Vessel Tasks

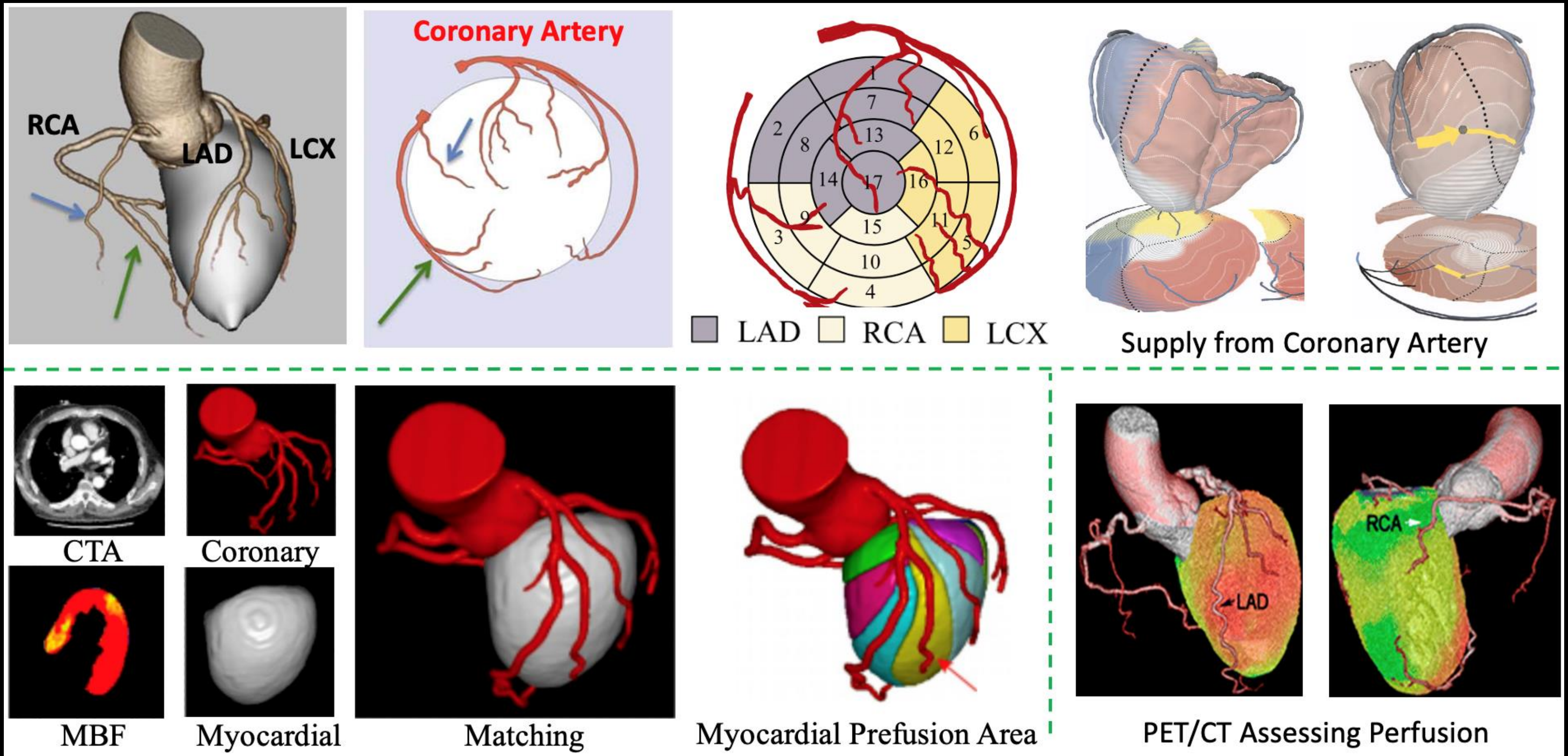
# CVD Analysis Pipeline

## Overview of the Cardiac Image Analysis Pipeline and Examples



# Joint Analysis

Examples of connections of non-vessel and vessel structures



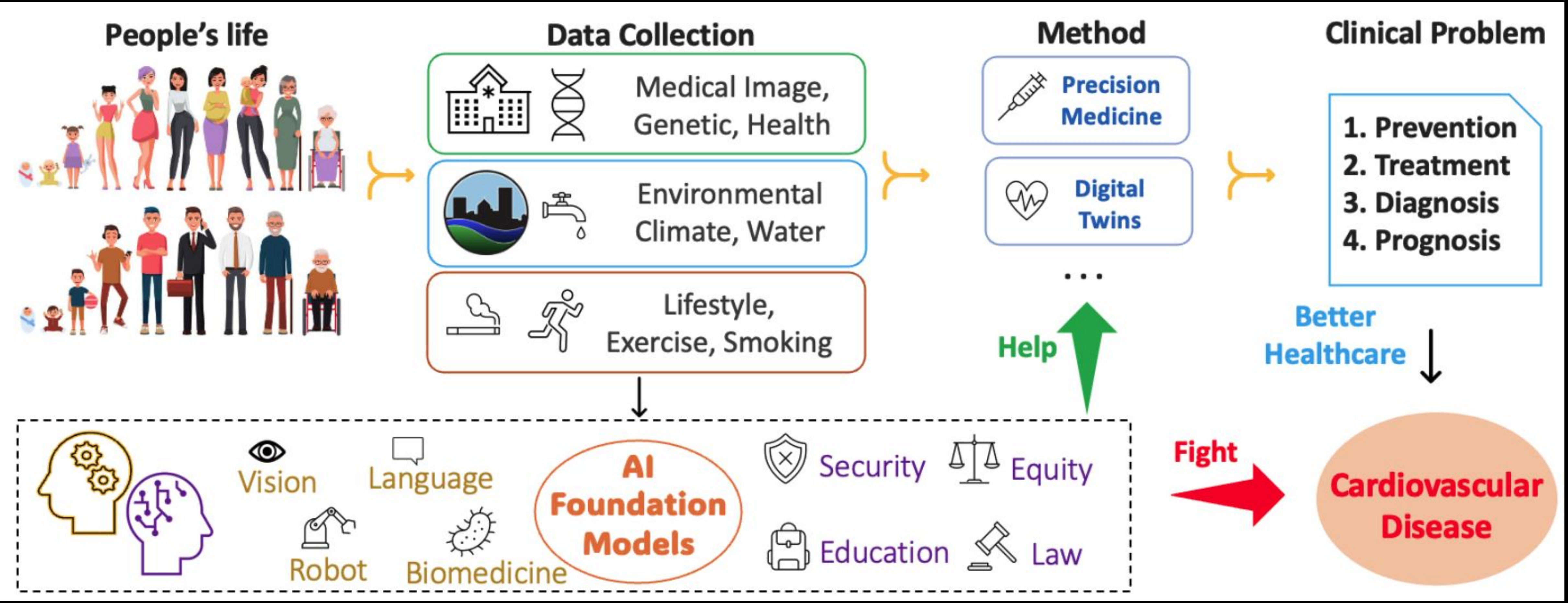

Top: Coronary Artery with corresponding LV regions for providing blood

Bottom (right): PET/CT assessing perfusion and Coronary Artery anatomy

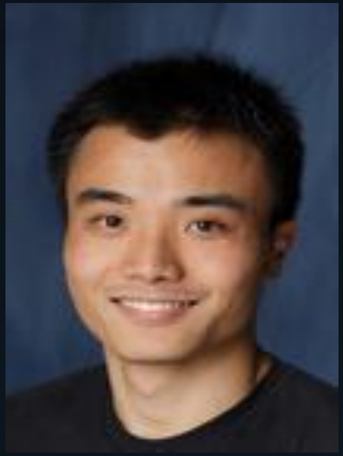
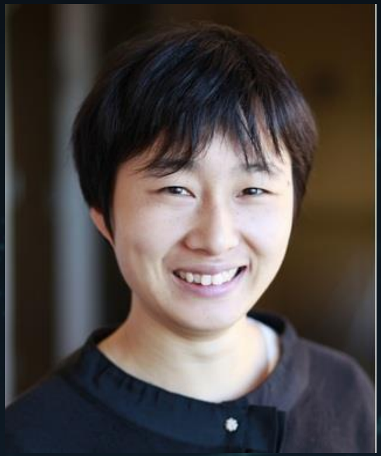
Bottom (left): Determination of Myocardial Perfusion Territory

# Future of AI for CVD

Exploring the future with AI Foundation Models



# Acknowledgement

**Funding:** U.S. NIH Grants MH116527, NIA-AG082938-01, U01AG079847, and R01AR082684.
Gilling Innovative Lab on Generative AI.

We thank Drs. Bingxin Zhao, Tengfei Li, Yun Li, Jason Stein, Patrick Sullivan and other members of the UNC BIG-S2 lab (https://med.unc.edu/bigs2/) for processing the neuroimaging data.

UK Biobank resource application number: 22783.

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